(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 3 587 446 A1**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
01.01.2020 Bulletin 2020/01

(21) Application number: **19175730.1**

(22) Date of filing: **18.09.2015**

(51) Int Cl.:
C07K 14/715 *(2006.01)* ***C07K 14/54*** *(2006.01)*
C07K 19/00 *(2006.01)* ***C12N 15/867*** *(2006.01)*
C07K 14/705 *(2006.01)* ***C07K 14/725*** *(2006.01)*
C07K 14/73 *(2006.01)* *C12N 5/0783* *(2010.01)*
A61K 38/00 *(2006.01)*

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Validation States:
MA

(30) Priority: **19.09.2014 US 201462053068 P**

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
15775539.8 / 3 194 433

(71) Applicant: **City of Hope**
Duarte, CA 91010 (US)

(72) Inventors:
- **Brown, Christine, E.**
Duarte, CA 91010 (US)
- **FORMAN, Stephen, J.**
Duarte, CA 91010 (US)

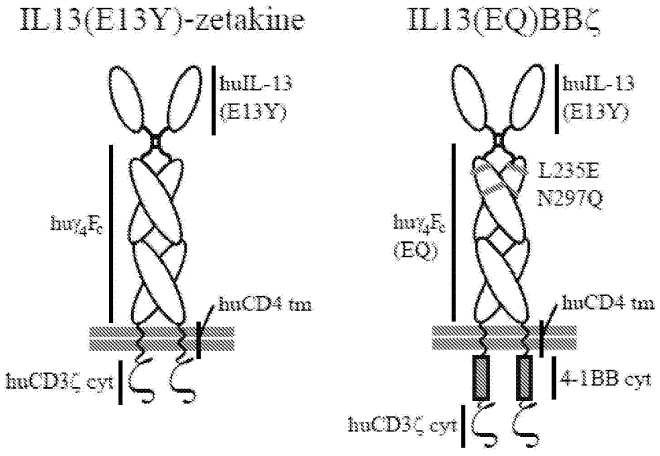
(74) Representative: **Ammelburg, Jan Moritz**
c/o Fish & Richardson P.C.
Highlight Business Towers
Mies-van-der-Rohe-Straße 8
80807 München (DE)

Remarks:
•Claims filed after the date of receipt of the divisional application (Rule 68(4) EPC).
•This application was filed on 21-05-2019 as a divisional application to the application mentioned under INID code 62.

(54) **COSTIMULATORY CHIMERIC ANTIGEN RECEPTOR T CELLS TARGETING IL13 R ALPHA 2**

(57) Chimeric transmembrane immunoreceptors (CAR) which include an extracellular domain that includes IL-13 or a variant thereof that binds interleukin-13Rα2 (IL13Rα2), a transmembrane region, a costimulatory domain and an intracellular signaling domain are described.

FIGURE 1



EP 3 587 446 A1

Description

BACKGROUND

[0001] Tumor-specific T cell based immunotherapies, including therapies employing engineered T cells, have been investigated for anti-tumor treatment. In some cases the T cells used in such therapies do not remain active *in vivo* for a long enough period. In some cases, the tumor-specificity of the T cells is relatively low. Therefore, there is a need in the art for tumor-specific cancer therapies with longer term anti-tumor functioning.

[0002] Malignant gliomas (MG), which include anaplastic astrocytoma (AA-grade III) and glioblastoma (GBM-grade IV), have an incidence rate of approximately 20,000 new cases diagnosed annually in the United States. According to the American Brain Tumor Association total prevalence of individuals living with a malignant brain tumor, based on United States 2010 census data, is roughly 140,000 persons. Although MG is a rare disease, it is highly aggressive and heterogeneous with respect to its malignant behavior and nearly uniformly lethal. Current standard-of-care therapies for high-grade MG yield only short term benefits, and these brain tumors are virtually incurable. Indeed, even with modern surgical and radiotherapeutic techniques, which often exacerbate the already severe morbidities imposed by location in the central nervous system (CNS), the 5-year survival rates are quite low. Furthermore, for the majority of patients who relapse with disease, there are few therapeutic options. Thus, there is a significant need for more effective therapies, particularly for those patients that have recurred/progressed following frontline therapies, and participation of this patient population in clinical trials is warranted.

[0003] Adoptive T cell therapy (ACT) utilizing chimeric antigen receptor (CAR) engineered T cells may provide a safe and effective way to reduce recurrence rates of MG, since CAR T cells can be engineered to specifically recognize antigenically-distinct tumor populations (Cartellieri et al. 2010 J Biomed Biotechnol 2010:956304; Ahmed et al. 2010 Clin Cancer Res 16:474; Sampson et al. 2014 Clin Cancer Res 20:972; Brown et al. 2013 Clin Cancer Res 2012 18:2199; Chow et al. 2013 Mol Ther 21:629), and T cells can migrate through the brain parenchyma to target and kill infiltrative malignant cells (Hong et al. 2010 Clin Cancer Res 16:4892; Brown et al. 2007 J Immunol 179:3332; Hong et al. 2010 Clin Cancer Res 16:4892; Yaghoubi 2009 Nat Clin PRact Oncol 6:53). Preclinical studies have demonstrated that IL13Rα2-targeting CAR+ T cells exhibit potent major histocompatibility complex (MHC)-independent, IL13Rα2-specific cytolytic activity against both stem-like and differentiated glioma cells, and induce regression of established glioma xenografts *in vivo* (Kahlon et al. 2004 Cancer Res 64:9160; Brown et al. 2012 Clin Cancer Res 18:2199).

SUMMARY

[0004] Described herein are chimeric transmembrane immunoreceptors (chimeric antigen receptors or "CARs") which comprise an extracellular domain, a transmembrane region and an intracellular signaling domain. The extracellular domain is made up of an IL-13 ligand that binds interleukin-13Rα2 (IL13Rα2) and, optionally, a spacer, comprising, for example a portion human Fc domain. The transmembrane portion includes a CD4 transmembrane domain, a CD8 transmembrane domain, a CD28 transmembrane domain, a CD3 transmembrane domain or a 4IBB transmembrane domain. The intracellular signaling domain includes the signaling domain from the zeta chain of the human CD3 complex (CD3ζ) and one or more costimulatory domains, e.g., a 4-1BB costimulatory domain. The extracellular domain enables the CAR, when expressed on the surface of a T cell, to direct T cell activity to those cells expressing IL13Rα2, a receptor expressed on the surface of tumor cells, including glioma. Importantly, the IL13Rα2 binding portion of the CAR includes an amino acid modification, such as an E13Y mutation, that increases binding specificity. The inclusion of a costimulatory domain, such as the 4-1BB (CD137) costimulatory domain in series with CD3ζ in the intracellular region enables the T cell to receive co-stimulatory signals. T cells, for example, patient-specific, autologous T cells can be engineered to express the CARs described herein and the engineered cells can be expanded and used in ACT. Various T cell subsets can be used. In addition, the CAR can be expressed in other immune cells such as NK cells. Where a patient is treated with an immune cell expressing a CAR described herein the cell can be an autologous or allogenic T cell. In some cases the cells used are CD4+ and CD8+ central memory T cells (T_{CM}), which are CD45RO+CD62L+, and the use of such cells can improve long-term persistence of the cells after adoptive transfer compared to the use of other types of patient-specific T cells.

[0005] Described herein is a nucleic acid molecule encoding a chimeric antigen receptor (CAR)r, wherein the chimeric antigen receptor comprises: human IL-13 or a variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications; a transmembrane domain selected from: a CD4 transmembrane domain or variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications, a CD8 transmembrane domain or variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications, a CD28 transmembrane domain or a variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications, and a CD3ζ transmembrane domain or a variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications; a costimulatory domain; and CD3 ζ signaling domain of a variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications.

[0006] In various embodiments the costimulatory domain is selected from the group consisting of: a CD28 costimulatory

domain or a variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications, a 4-IBB costimulatory domain or a variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications and an OX40 costimulatory domain or a variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications. In certain embodiments, a 4IBB costimulatory domain or a variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications in present.

[0007] Additional embodiment the CAR comprises: a variant of a human IL13 having 1-10 amino acid modification that increase binding specificity for IL13Rα2 versus IL13Rα1; the human IL-13 or variant thereof is an IL-13 variant comprising the amino acid sequence of SEQ ID NO:3 with 1 to 5 amino acid modifications, provided that the amino acid at position 11 of SEQ ID NO:3 other than E; two different costimulatory domains selected from the group consisting of: a CD28 costimulatory domain or a variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications, a 4IBB costimulatory domain or a variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications and an OX40 costimulatory domain or a variant thereof having 1-10 (e.g., 1 or 2) amino acid modifications; two different costimulatory domains selected from the group consisting of: a CD28 costimulatory domain or a variant thereof having 1-2 amino acid modifications, a 4IBB costimulatory domain or a variant thereof having 1-2 amino acid modifications and an OX40 costimulatory domain or a variant thereof having 1-2 amino acid modifications; human IL-13 or a variant thereof having 1-2 amino acid modifications; a transmembrane domain selected from: a CD4 transmembrane domain or variant thereof having 1-2 amino acid modifications, a CD8 transmembrane domain or variant thereof having 1-2 amino acid modifications, a CD28 transmembrane domain or a variant thereof having 1-2 amino acid modifications, and a CD3ζ transmembrane domain or a variant thereof having 1-2 amino acid modifications; a costimulatory domain; and CD3ζ signaling domain of a variant thereof having 1-2 amino acid modifications; a spacer region located between the IL-13 or variant thereof and the transmembrane domain (e.g., the spacer region comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 14-20, 50 and 52); the spacer comprises an IgG hinge region; the spacer region comprises 10-150 amino acids; the 4-1BB signaling domain comprises the amino acid sequence of SEQ ID NO:6; the CD3ζ signaling domain comprises the amino acid sequence of SEQ ID NO:7; and a linker of 3 to 15 amino acids that is located between the costimulatory domain and the CD3 ζ signaling domain or variant thereof. In certain embodiments where there are two costimulatory domains, one is an 4-IBB costimulatory domain and the other a costimulatory domain selected from: CD28 and CD28gg

[0008] In some embodiments: nucleic acid molecule expresses a polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 10, 31-48 and 52; the chimeric antigen receptor comprises a IL-13/IgG4/CD4t/41-BB region comprising the amino acid of SEQ ID NO:11 and a CD3 ζ signaling domain comprising the amino acid sequence of SEQ ID NO:7; and the chimeric antigen receptor comprises the amino acid sequence of SEQ ID NOs: 10, 31-48 and 52.

[0009] Also disclosed is a population of human T cells transduced by a vector comprising an expression cassette encoding a chimeric antigen receptor, wherein chimeric antigen receptor comprises: human IL-13 or a variant thereof having 1-10 amino acid modifications; a transmembrane domain selected from: a CD4 transmembrane domain or variant thereof having 1-10 amino acid modifications, a CD8 transmembrane domain or variant thereof having 1-10 amino acid modifications, a CD28 transmembrane domain or a variant thereof having 1-10 amino acid modifications, and a CD3ζ transmembrane domain or a variant thereof having 1-10 amino acid modifications; a costimulatory domain; and CD3 ζ signaling domain of a variant thereof having 1-10 amino acid modifications. In various embodiments: the population of human T cells comrpise a vector expressing a chimeric antigen receptor comprising an amino acid sequence selected from SEQ ID NOs: 10, 31-48 and 52; the population of human T cells are comprises of central memory T cells (Tcm cells) (e.g., at least 20%, 30%, 40%, 50% 60%, 70%, 80% of the cells are Tcm cells; at least 15%, 20%, 25%, 30%, 35% of the Tcm cells are CD4+ and at least 15%, 20%, 25%, 30%, 35% of the Tcm cells are CD8+ cells).

[0010] Also described is a method of treating cancer in a patient comprising administering a population of autologous or allogeneic human T cells (e.g., autologous or allogenic T cells comprising Tcm cells, e.g., at least 20%, 30%, 40%, 50% 60%, 70%, 80% of the cells are Tcm cells; at least 15%, 20%, 25%, 30%, 35% of the Tcm cells are CD4+ and at least 15%, 20%, 25%, 30%, 35% of the Tcm cells are CD8+ cells) transduced by a vector comprising an expression cassette encoding a chimeric antigen receptor, wherein chimeric antigen receptor comprises an amino acid sequence selected from SEQ ID NOs: 10, 31-48 and 52. In various embodiments: the population of human T cells comprise central memory T cells; the cancer is glioblastoma; and the transduced human T cells where prepared by a method comprising obtaining T cells from the patient, treating the T cells to isolate central memory T cells, and transducing at least a portion of the central memory cells to with a viral vector comprising an expression cassette encoding a chimeric antigen receptor, wherein chimeric antigen receptor comprises an amino acid sequence selected from SEQ ID NOs: 10, 31-48 and 52.

[0011] Also described is: a nucleic acid molecule encoding an polypeptide comprising an amino acid sequence that is at least 95% identical to an amino acid sequence selected from SEQ ID NO:10 and SEQ ID NOs: 10, 31-48 and 52; a nucleic acid molecule encoding an polypeptide comprising an amino acid sequence that is identical to an amino acid sequence selected from SEQ ID NO: 10, 31-48 and 52 except for the presence of no more than 5 amino acid substitutions, deletions or insertions; a nucleic acid molecule encoding an polypeptide comprising an amino acid sequence that is identical to an amino acid sequence selected from SEQ ID NO:10 and SEQ ID NOs: 10, 31-48 and 52 except for the presence of no more than 5 amino acid substitutions; and a nucleic acid molecule encoding an polypeptide comprising an amino acid sequence that is identical to an amino acid sequence selected from SEQ ID NO:10 and SEQ ID NOs:

10, 31-48 and 52 except for the presence of no more than 2 amino acid substitutions.

[0012] Certain CAR described herein, for example, the IL13(EQ)BBζ CAR and the IL13(EQ)CD28- BBζ CAR, have certain beneficial characteristics compared to certain other IL13-targeted CAR. For example, they have improved selectivity for IL13Rα, elicit lower Th2 cytokine production, particularly lower IL13 production.

[0013] T cells expressing a CAR targeting IL13Rα2 can be useful in treatment of cancers such as glioblastoma, as well as other cancer that expresses IL13Rα2 which include but are not limited to medulloblastoma, breast cancer, head and neck cancer, kidney cancer, ovarian cancer and Kaposi's sarcoma. Thus, this disclosure includes methods for treating cancer using T cells expressing a CAR described herein.

[0014] This disclosure also nucleic acid molecules that encode any of the CARs described herein (e.g., vectors that include a nucleic acid sequence encoding one of the CARs) and isolated T lymphocytes that express any of the CARs described herein.

[0015] The CAR described herein can include a spacer region located between the IL13 domain and the transmembrane domain. A variety of different spacers can be used. Some of them include at least portion of a human Fc region, for example a hinge portion of a human Fc region or a CH3 domain or variants thereof. Table 1 below provides various spacers that can be used in the CARs described herein.

Table 1: Examples of Spacers

Name	Length	Sequence
a3	3 aa	AAA
linker	10 aa	GGGSSGGGSG (SEQ ID NO:14)
IgG4 hinge (S→P) (S228P)	12 aa	ESKYGPPCPPCP (SEQ ID NO:15)
IgG4 hinge	12 aa	ESKYGPPCPSCP (SEQ ID NO:52)
IgG4 hinge + linker	22 aa	ESKYGPPCPPCPGGGSSGGGSG (SEQ ID NO:16)
CD28 hinge	39 aa	IEVMYPPPYLDNEKSNGTIIHVKGKHL CPSPLFPGPSKP (SEQ ID NO:17)
CD8 hinge-48aa	48 aa	AKPTTTPAPRPPTPAPTIASQPLSLRPE ACRPAAGGAVHTRGLDFACD (SEQ ID NO:18)
CD8 hinge-45aa	45aa	TTTPAPRPPTPAPTIASQPLSLRPEACR PAAGGAVHTRGLDFACD (SEQ ID NO:19)
IgG4(HL-CH3)	129 aa	ESKYGPPCPPCPGGGSSGGGSGGQPR EPQVYTLPPSQEEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNV FSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO:20)

(continued)

Name	Length	Sequence
IgG4(L235E,N297Q)	229 aa	ESKYGPPCPSCPAPEFEGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHQAKTKPREEQFN STYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVY TLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK (SEQ ID NO:4)
IgG4(S228P, L235E,N297Q)	229 aa	ESKYGPPCPPCPAPEFEGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHQAKTKPREEQFN STYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVY TLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK (SEQ ID NO:51)
IgG4(CH3)	107 aa	GQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLS LGK (SEQ ID NO:50)

Some spacer regions include all or part of an immunoglobulin (e.g., IgG1, IgG2, IgG3, IgG4) hinge region, i.e., the sequence that falls between the CH1 and CH2 domains of an immunoglobulin, e.g., an IgG4 Fc hinge or a CD8 hinge. Some spacer regions include an immunoglobulin CH3 domain or both a CH3 domain and a CH2 domain. The immunoglobulin derived sequences can include one ore more amino acid modifications, for example, 1, 2, 3, 4 or 5 substitutions, e.g., substitutions that reduce off-target binding.

[0016] An "amino acid modification" refers to an amino acid substitution, insertion, and/or deletion in a protein or peptide sequence. An "amino acid substitution" or "substitution" refers to replacement of an amino acid at a particular position in a parent peptide or protein sequence with another amino acid. A substitution can be made to change an amino acid in the resulting protein in a non-conservative manner (i.e., by changing the codon from an amino acid belonging to a grouping of amino acids having a particular size or characteristic to an amino acid belonging to another grouping) or in a conservative manner (i.e., by changing the codon from an amino acid belonging to a grouping of amino acids having a particular size or characteristic to an amino acid belonging to the same grouping). Such a conservative change generally leads to less change in the structure and function of the resulting protein. The following are examples of various groupings of amino acids: 1) Amino acids with nonpolar R groups: Alanine, Valine, Leucine, Isoleucine, Proline, Phenylalanine, Tryptophan, Methionine; 2) Amino acids with uncharged polar R groups: Glycine, Serine, Threonine, Cysteine, Tyrosine, Asparagine, Glutamine; 3) Amino acids with charged polar R groups (negatively charged at pH 6.0): Aspartic acid, Glutamic acid; 4) Basic amino acids (positively charged at pH 6.0): Lysine, Arginine, Histidine (at pH 6.0). Another grouping may be those amino acids with phenyl groups: Phenylalanine, Tryptophan, and Tyrosine.

[0017] In certain embodiments, the spacer is derived from an IgG1, IgG2, IgG3, or IgG4 that includes one or more amino acid residues substituted with an amino acid residue different from that present in an unmodified spacer. The one or more substituted amino acid residues are selected from, but not limited to one or more amino acid residues at positions

220, 226, 228, 229, 230, 233, 234, 235, 234, 237, 238, 239, 243, 247, 267, 268, 280, 290, 292, 297, 298, 299, 300, 305, 309, 218, 326, 330, 331, 332, 333, 334, 336, 339, or a combination thereof. In this numbering scheme, described in greater detail below, the first amino acid in the IgG4(L235E,N297Q) spacer in Table 1 is 219 and the first amino acid in the IgG4(HL-CH3) spacer in Table 1 is 219 as is the first amino acid in the IgG hinge sequence and the IgG4 hinge linker (HL) sequence in Table 1

[0018] In some embodiments, the modified spacer is derived from an IgG1, IgG2, IgG3, or IgG4 that includes, but is not limited to, one or more of the following amino acid residue substitutions: C220S, C226S, S228P, C229S, P230S, E233P, V234A, L234V, L234F, L234A, L235A, L235E, G236A, G237A, P238S, S239D, F243L, P247I, S267E, H268Q, S280H, K290S, K290E, K290N, R292P, N297A, N297Q, S298A, S298G, S298D, S298V, T299A, Y300L, V305I, V309L, E318A, K326A, K326W, K326E, L328F, A330L, A330S, A331S, P331S, I332E, E333A, E333S, E333S, K334A, A339D, A339Q, P396L, or a combination thereof.

[0019] In certain embodiments, the modified spacer is derived from IgG4 region that includes one or more amino acid residues substituted with an amino acid residue different from that present in an unmodified region. The one or more substituted amino acid residues are selected from, but not limited to, one or more amino acid residues at positions 220, 226, 228, 229, 230, 233, 234, 235, 234, 237, 238, 239, 243, 247, 267, 268, 280, 290, 292, 297, 298, 299, 300, 305, 309, 218, 326, 330, 331, 332, 333, 334, 336, 339, or a combination thereof.

[0020] In some embodiments, the modified spacer is derived from an IgG4 region that includes, but is not limited to, one or more of the following amino acid residue substitutions: 220S, 226S, 228P, 229S, 230S, 233P, 234A, 234V, 234F, 234A, 235A, 235E, 236A, 237A, 238S, 239D, 243L, 247I, 267E, 268Q, 280H, 290S, 290E, 290N, 292P, 297A, 297Q, 298A, 298G, 298D, 298V, 299A, 300L, 305I, 309L, 318A, 326A, 326W, 326E, 328F, 330L, 330S, 331S, 331S, 332E, 333A, 333S, 333S, 334A, 339D, 339Q, 396L, or a combination thereof, wherein the amino acid in the unmodified spacer is substituted with the above identified amino acids at the indicated position.

[0021] For amino acid positions in immunoglobulin discussed herein, numbering is according to the EU index or EU numbering scheme (Kabat et al. 1991 Sequences of Proteins of Immunological Interest, 5th Ed., United States Public Health Service, National Institutes of Health, Bethesda, hereby entirely incorporated by reference). The EU index or EU index as in Kabat or EU numbering scheme refers to the numbering of the EU antibody (Edelman et al. 1969 Proc Natl Acad Sci USA 63:78-85).

[0022] A variety of transmembrane domains can be used in CAR directed against IL13Ra2. Table 2 includes examples of suitable transmembrane domains. Where a spacer domain is present, the transmembrane domain is located carboxy terminal to the spacer domain.

Table 2: Examples of Transmembrane Domains

Name	Accession	Length	Sequence
CD3z	J04132.1	21 aa	LCYLLDGILFIYGVILTALFL (SEQ ID NO:21)
CD28	NM_ 006139	27aa	FWVLVVVGGVLACYSLLVTVAFIIFWV (SEQ ID NO:22)
CD28(M)	NM_ 006139	28aa	MFWVLVVVGGVLACYSLLVTVAFIIFWV (SEQ ID NO:22)
CD4	M35160	22aa	MALIVLGGVAGLLLFIGLGIFF (SEQ ID NO:5)
CD8tm	NM_001768	21aa	IYIWAPLAGTCGVLLLSLVIT (SEQ ID NO:23)
CD8tm2	NM_001768	23aa	IYIWAPLAGTCGVLLLSLVITLY (SEQ ID NO:24)
CD8tm3	NM_001768	24aa	IYIWAPLAGTCGVLLLSLVITLYC (SEQ ID NO:25)
41BB	NM_001561	27aa	IISFFLALTSTALLFLLFF LTLRFSVV (SEQ ID NO:26)

Many of the CAR described herein include one or more (e.g., two) costimulatory domains. The costimulatory domain(s) are located between the transmembrane domain and the CD3ζ signaling domain. Table 3 includes examples of suitable costimulatory domains together with the sequence of the CD3ζ signaling domain.

Table 3: Examples of Costimulatory Domains

Name	Accession	Length	Sequence
CD3C	J04132.1	113 aa	RVKFSRSADAPAYQQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAYSEIGMKGERRR GKGHDGLYQGLSTATKDTYDALHMQAL PPR
CD28	NM_ 006139	42aa	RSKRSRLLHSDYMNMTPRRPGPTRKHYQ PYAPPRDFAAYRS (SEQ ID NO: 27)
CD28gg*	NM_006139	42aa	RSKRSRGGHSDYMNMTPRRPGPTRKHY QPYAPPRDFAAYRS (SEQ ID NO:28)
41BB	NM_001561	42 aa	KRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCEL (SEQ ID NO:29)
OX40		42 aa	ALYLLRRDQRLPPDAHKPPGGGSFRTPIQ EEQADAHSTLAKI (SEQ ID NO:30)

DESCRIPTION OF DRAWINGS

[0023]

Figure 1 is a schematic depiction of IL13(E13Y)-zetakine CAR (Left) composed of the IL13Rα2-specific human IL-13 variant (huIL-13(E13Y)), human IgG4 Fc spacer (huγ_4F_c), human CD4 transmembrane (huCD4 tm), and human CD3ζ chain cytoplasmic (huCD3ζ cyt) portions as indicated. Also depicted is a IL13(EQ)BBζ CAR which is the same as the IL13(E13Y)-zetakine with the exception of the two point mutations, L235E and N297Q indicated in red, that are located in the CH2 domain of the IgG4 spacer, and the addition of a costimulatory 4-1BB cytoplasmic domain (4-1BB cyt).

Figures 2A-C depict certain vectors an open reading frames. **A** is a diagram of the cDNA open reading frame of the 2670 nucleotide IL13(EQ)BBZ-T2ACD19t construct, where the IL13Rα2-specific ligand IL13(E13Y), IgG4(EQ) Fc hinge, CD4 transmembrane, 4-1BB cytoplasmic signaling, three-glycine linker, and CD3ζ cytoplasmic signaling domains of the IL13(EQ)BBZ CAR, as well as the T2A ribosome skip and truncated CD19 sequences are indicated. The human GM-CSF receptor alpha and CD19 signal sequences that drive surface expression of the IL13(EQ)BBζ CAR and CD19t are also indicated. **B** is a diagram of the sequences flanked by long terminal repeats (indicated by 'R') that will integrate into the host genome. **C** is a map of the IL13(EQ)BBZ-T2A-CD19t_epHIV7 plasmid.

Figure 3 depicts the construction of pHIV7.

Figure 4 depicts the elements of pHIV7.

Figure 5 depicts a production scheme for IL13(EQ)BBζ/CD19t+ T_{CM}.

Figures 6A-C depicts the results of flow cytometric analysis of surface transgene and T cell marker expression. IL13(EQ)BBζ/CD19t+ T_{CM} HD006.5 and HD187.1 were co-stained with anti-IL13-PE and anti-CD8-FITC to detect CD8+ CAR+ and CD4+ (i.e., CD8 negative) CAR+ cells (**A**), or anti-CD 19-PE and anti-CD4-FITC to detect CD4+ CD19t+ and CD8+ (i.e., CD4 negative) CAR+ cells (**B**). IL13(EQ)BBζ/CD19t+ T_{CM} HD006.5 and HD187.1 stained with fluorochromeconjugatedanti-CD3, TCR, CD4, CD8, CD62L and CD28 (grey histograms) or isotype controls (black histograms) (C). In all cases the percentages based on viable lymphocytes (DAPI negative) stained above isotype.

Figures 7A-B depict the *in vitro* functional characterization of IL13Rα2-specific effector function of IL13(EQ)BBZ+

T_{CM}. IL13(EQ)BBZ/CD19t+ T_{CM} HD006.5 and HD187.1 were used as effectors in a 6-hour ^{51}Cr release assay using a 10:1 E:T ratio based on CD19t expression. The IL13Rα2-positive tumor targets were K562 engineered to express IL13Rα2 (K562-IL13Rα2) and primary glioma line PBT030-2, and the IL13Rα2-negative tumor target control was K562 parental line (**A**). IL13(EQ)BBZ/CD19t+ T_{CM} HD006.5 and HD187.1 were evaluated for antigen-dependent cytokine production following overnight co-culture at a 10:1 E:T ratio with IL13Rα2-positive and negative targets. Cytokine levels were measured using the Bio-Plex Pro Human Cytokine TH1/TH2 Assay kit and INF-γ are reported (**B**).

Figures 8A-C depict the result of studies demonstrating the regression of established glioma tumor xenografts after adoptive transfer of IL13(EQ)BBζ/CD19t+ T_{CM}. EGFP-ffLuc+ PBT030-2 tumor cells (1×10^5) were stereotactically implanted into the right forebrain of NSG mice. On day 5, mice received either $2x10^6$ IL13(EQ)BBζ/CD19t+ T_{CM} ($1.1x10^6$ CAR+; n=6), $2x10^6$ mock TCM (no CAR; n=6) or PBS (n=6). Representative mice from each group showing relative tumor burden using Xenogen Living Image (**A**). Quantification of ffLuc flux (photons/sec) shows that IL13(EQ)BBζ/CD19t+ T_{CM} induce tumor regression as compared to mock-transduced T_{CM} and PBS (#p<0.02, *p<0.001, repeated measures ANOVA) (**B**). Kaplan Meier survival curve (n=6 per group) demonstrating significantly improved survival (p=0.0008; log-rank test) for mice treated with IL13(EQ)BBζ/CD19t+ T_{CM} (**C**)

Figures 9A-C depict the results of studies comparing ant-tumor efficacy of IL13(EQ)BBZ T_{CM} and IL13-zetakine CTL clones. EGFP-ffLuc+ PBT030-2 TSs (1×10^5) were stereotactically implanted into the right forebrain of NSG mice. On day 8, mice received either $1.6x10^6$ mock T_{CM} (no CAR), 1.0×10^6 CAR+ IL13(EQ)BBζ T_{CM} (1.6×10^6 total T cells; 63% CAR), $1.0x10^6$ IL13-zetakine CD8+ CTL cl. 2D7 (clonal CAR+), or no treatment (n=6 per group). Representative mice from each group showing relative tumor burden using Xenogen Living Image (**A**). Linear regression lines of natural log of ffLuc flux (photons/sec) over time, P-values are for group by time interaction comparisons (**B**). Kaplan Meier survival analysis (n= 6 per group) demonstrate significantly improved survival (p=0.02; log-rank test) for mice treated with IL13(EQ)BBζ T_{CM} as compared to IL13-zetakine CD8+ CTL cl. 2D7 (**C**).

Figures 10A-C depict the results of studies comparing ant-tumor efficacy of IL13(EQ)BBζ T_{CM} and IL13-zetakine CTL clones. EGFP-ffLuc+ PBT030-2 TSs (1×10^5) were stereotactically implanted into the right forebrain of NSG mice. On day 8, mice received either $1.3x10^6$ mock T_{CM} (no CAR; n=6), 1.0, 0.3 or $0.1x10^6$ CAR+ IL13(EQ)BBζ T_{CM} (78% CAR+; n=6-7), 1.0, 0.3 or $0.1x10^6$ IL13-zetakine CD8+ CTL cl. 2D7 (clonal CAR+; n=6-7), or no treatment (n=5). Xenogen imaging of representative mice from each group showing relative tumor burden (**A**). Linear regression lines of natural log of ffLuc flux (photons/sec) shows that IL13(EQ)BBζ T_{CM} achieve superior tumor regression as compared to first-generation IL13-zetakine CTL cl. 2D7, mock T_{CM} and tumor only (**B**). Average flux per group at day 27 post tumor injection demonstrating that the $0.1x10^6$ IL13(EQ)BBζ T_{CM} dose outperforms the ten-fold higher $1.0x10^6$ dose of IL13-zetakine CD8+ CTL cl. 2D7 (p = 0.043; Welch two sample t- test) (**C**).

Figure 11 depicts the results of studies demonstrating IL13(EQ)BBζ Tcm display improved persistence compared IL13-zetakine CTL clones. CD3 immunohistochemistry evaluating T cell persistence at the tumor site 7-days post T cell infusion. Significant numbers of T cells are detected for IL13(EQ)BBζ Tcm (top panel). By contrast, very few viable CD3+ IL13-zetakine T cells are detected (bottom panel).

Figures 12A-D depict the results of experiments comparing route of CAR+ T cell delivery (i.c. versus i.v.) for large established tumors. EGFP-ffLuc+ PBT030-2 TSs (1×10^5) were implanted into the right forebrain of NSG mice. On days 19 and 26, mice were injected i.v. through the tail vein with either $5x10^6$ CAR+ IL13(EQ)BBζ+ Tcm ($11.8x10^6$ total cells; n=4), or mock Tcm ($11.8x10^6$ cells; n=4). Alternatively, on days 19, 22, 26 and 29 mice were injected i.c. with either $1x10^6$ CAR+ IL13(EQ)BBζ+ Tcm ($2.4x10^6$ total cells; n=4), or mock Tcm ($2.4x10^6$ cells; n=5). Average ffLuc flux (photons/sec) over time shows that i.c. delivered IL13(EQ)BBζ Tcm mediates tumor regression of day 19 tumors. By comparison, i.v. delivered T cells do not shown reduction in tumor burden as compared to untreated or mock Tcm controls (**A**). Kaplan Meier survival curve demonstrates improved survival for mice treated i.c. IL13(EQ)BBZ Tcm as compared to mice treated with i.v. administered CAR+ Tcm (p = 0.0003 log rank test) (**B**). Representative H&E and CD3 IHC of mice treated i.v. (**C**) versus i.c. (**D**) with IL13(EQ)BBZ+ Tcm. CD3+ T cells were only detected in the i.c. treated group, with no CD3+ cells detected in the tumor or surrounding brain parenchyma for i.v. treated mice.

Figures 13A-B depict the results of studies showing that CAR+ T cell injected intracranially, either intratumoral (i.c.t.) or intraventricular (i.c.v.), can traffic to tumors on the opposite hemisphere. EGFP-ffLuc+ PBT030-2 TSs (1×105) were stereotactically implanted into the right and left forebrains of NSG mice. On day 6, mice were injected i.c. at the right tumor site with $1.0x10^6$ IL13(EQ)BBζ+ Tcm (1.6x106 total cells; 63% CAR; n=4). Schematic of

multifocal glioma experimental model (**A**). CD3 IHC showing T cells infiltrating both the right and left tumor sites (**B**).

Figures 14A-C depict the results of a series of studies evaluating costimulatory domains of IL13Rα2-specific CAR. Schematic of IL13Ra2-specific CAR constructs comparing various intracellular endo/signaling domains, including the first generation CD3z CAR lacking costimulation, versus second generation CARs incorporating either 4-1BB or CD28, versus a third generation CAR containing both CD28 and 41BB. All CAR cassettes also contain the T2A ribosomal skip and truncated CD19 (CD19t) sequences as a marker for transduced cells (**A**). CD4 and CD8 TCM were lentivirally transduced and CAR-expressing T cells were immunomagnetically enriched via anti-CD19. CD19 and IL13 (i.e., CAR) expression levels as measured by flow cytometry (**B**). Stability of each CAR construct was determined by dividing the CAR (IL13) mean flourescence intenstity (MFI) by that of the transduction marker (CD19t) (**C**). The 4-1BB containing CARs demonstrated the lowest expression levels as compared to the CD19t transduction marker.

Figures 15A-B depict the results of studies demonstrating that IL13Rα2-specific CAR containing the 4-1BB costimulatory domain produce less Th1 and Th2 cytokines. The ability of the indicated mock-transduced or CAR-expressing T cells to kill IL13Rα2-expressing PBT030-2 tumor cell targets was determined in a 4-hour 51Cr-release assay at the indicated effector:target ratios. Mean % chromium release + S.D. of triplicate wells are depicted (**A**). As expected, mock-transduced T cells did not efficiently lyse the targets. In contrast, all CAR-expressing T cells lysed the tumor cells in a similar manner. The indicated mock-transduced or CAR-expressing T cells were co-cultured overnight with IL13Rα2-expressing PBT030-2 tumor cells at a 10:1 ratio and supernatants were analyzed for IL-13 and IFN-γ levels by cytometric bead array (**B**). Means + S.D. of triplicate wells are depicted. Interestingly, T cells expressing the zeta, 41BB-zeta or CD28-41BB-zeta CARs exhibited lower antigen-stimulated cytokine production than T cells expressing the CD28-zeta CAR.

Figures 16A-C depict the results of a series of studies of the in vivo efficacy of IL13Rα2-specific CARs. NSG mice received an intracranial injection of ffLuc+ PBT030-2 tumor cells on day 0, and were randomized into 6 groups (n = 9-10 mice per group) for i.c. treatment with either PBS (Tumor Only), mock-transduced T cells or T cells expressing the indicated IL13Rα2-specific CAR on day 8. Quantitative bioluminescence imaging was then carried out to monitor tumor growth over time. Bioluminescence images for representative mice in each group (**A**). Mean + S.E. of total flux levels of luciferase activity over time in each group (**B**). Flux levels for each mouse at Day 27. All groups treated with IL13Rα2-specific CAR T cells, except those treated with T cells expressing the CD28-CAR, show statistically-significant reduction in tumor volume compared to mice treated with mock-transduced T cells (C)

Figure 17 depicts the amino acid sequence of IL13(EQ)BBζ/CD19t+ (SEQ ID NO:10).

Figure 18 depicts a sequence comparison of IL13(EQ)41BBζ[IL13{EQ}41BBζ T2A-CD19t_epHIV7; pF02630] (SEQ ID NO:12) and CD19Rop_epHIV7 (pJ01683) (SEQ ID NO:13).

Figure 19 depicts the amino acid sequence of IL13(EmY)-CD8h3-CD8tm2-41BB Zeta (SEQ ID NO:31 with GMSCFRa signal peptide; SEQ ID NO:39 without GMSCFRa signal peptide).

Figure 20 depicts the amino acid sequence of IL13(EmY)-CD8h3-CD28tm-CD28gg-41BB-Zeta (SEQ ID NO:32 with GMSCFRa signal peptide; SEQ ID NO:40 without GMSCFRa signal peptide).

Figure 21 depicts the amino acid sequence of IL13(EmY)-IgG4(HL-CH3)-CD4tm-41BB-Zeta (SEQ ID NO:33 with GMSCFRa signal peptide; SEQ ID NO:41 without GMSCFRa signal peptide).

Figure 22 depicts the amino acid sequence of IL13(EmY)-IgG4(L235E,N297Q)-CD8tm-41BB-Zeta (SEQ ID NO:34 with GMSCFRa signal peptide; SEQ ID NO:42 without GMSCFRa signal peptide).

Figure 23 depicts the amino acid sequence of IL13(EmY)-Linker-CD28tm-CD28gg-41BB-Zeta (SEQ ID NO:35 with GMSCFRa signal peptide; SEQ ID NO:43without GMSCFRa signal peptide).

Figure 24 depicts the amino acid sequence of IL13(EmY)-HL-CD28m-CD28gg-41BB-Zeta (SEQ ID NO:36 with GMSCFRa signal peptide; SEQ ID NO:44 without GMSCFRa signal peptide).

Figure 25 depicts the amino acid sequence of IL13(EmY)-IgG4(HL-CH3)-CD28tm-CD28gg-41BB-Zeta (SEQ ID NO:37 with GMSCFRa signal peptide; SEQ ID NO:45 without GMSCFRa signal peptide).

Figure 26 depicts the amino acid sequence of IL13(EmY) IgG4(L235E,N297Q)-CD28tm-CD28gg-41BB-Zeta (SEQ ID NO:38 with GMSCFRa signal peptide; SEQ ID NO:46 without GMSCFRa signal peptide).

Figure 27 depicts the amino acid sequence of IL13(EmY)-CD8h3-CD8tm-41BB Zeta (SEQ ID NO:47 with GMSCFRa signal peptide; SEQ ID NO:48 without GMSCFRa signal peptide).

DETAILED DESCRIPTION

[0024] Described below is the structure, construction and characterization of various IL13Rα2-specific chimeric antigen receptors. A chimeric antigen (CAR) is a recombinant biomolecule that contains, at a minimum, an extracellular recognition domain, a transmembrane region, and an intracellular signaling domain. The term "antigen," therefore, is not limited to molecules that bind antibodies, but to any molecule that can bind specifically to a target. For example, a CAR can include a ligand that specifically binds a cell surface receptor. The extracellular recognition domain (also referred to as the extracellular domain or simply by the recognition element which it contains) comprises a recognition element that specifically binds to a molecule present on the cell surface of a target cell. The transmembrane region anchors the CAR in the membrane. The intracellular signaling domain comprises the signaling domain from the zeta chain of the human CD3 complex and optionally comprises one or more costimulatory signaling domains. CARs can both to bind antigen and transduce T cell activation, independent of MHC restriction. Thus, CARs are "universal" immunoreceptors which can treat a population of patients with antigen-positive tumors irrespective of their HLA genotype. Adoptive immunotherapy using T lymphocytes that express a tumor-specific CAR can be a powerful therapeutic strategy for the treatment of cancer.

[0025] One IL13Rα2-specific CAR described herein is referred to as IL13(EQ)BBζ. This CAR includes a variety of important features including: a IL13α2 ligand having an amino acid change that improves specificity of biding to IL13α2; the domain of CD137 (4-1BB) in series with CD3ζ to provide beneficial costimulation; and an IgG4 Fc region that is mutated at two sites within the CH2 region (L235E; N297Q) in a manner that reduces binding by Fc receptors (FcRs). Other CAR described herein contain a second costimulatory domain.

[0026] In some cases the CAR described herein, including the IL13(EQ)BBζ CAR can be produced using a vector in which the CAR open reading frame is followed by a T2A ribosome skip sequence and a truncated CD19 (CD19t), which lacks the cytoplasmic signaling tail (truncated at amino acid 323). In this arrangement, co-expression of CD19t provides an inert, non-immunogenic surface marker that allows for accurate measurement of gene modified cells, and enables positive selection of gene-modified cells, as well as efficient cell tracking and/or imaging of the therapeutic T cells in vivo following adoptive transfer. Co-expression of CD19t provides a marker for immunological targeting of the transduced cells in vivo using clinically available antibodies and/or immunotoxin reagents to selectively delete the therapeutic cells, and thereby functioning as a suicide switch.

[0027] Gliomas, express IL13 receptors, and in particular, high-affinity IL13 receptors. However, unlike the IL13 receptor, glioma cells overexpress a unique IL13Rα2 chain capable of binding IL13 independently of the requirement for IL4Rβ or γc44. Like its homolog IL4, IL13 has pleotropic immunoregulatory activity outside the CNS. Both IL13 and IL4 stimulate IgE production by B lymphocytes and suppress pro-inflammatory cytokine production by macrophages.

[0028] Detailed studies using autoradiography with radiolabeled IL13 have demonstrated abundant IL13 binding on nearly all malignant glioma tissues studied. This binding is highly homogeneous within tumor sections and in single cell analysis. However, molecular probe analysis specific for IL13Rα2 mRNA did not detect expression of the glioma-specific receptor by normal brain elements and autoradiography with radiolabeled IL13 also could not detect specific IL13 binding in the normal CNS. These studies suggest that the shared IL13Rα1/IL4β/γc receptor is not expressed detectably in the normal CNS. Therefore, IL13Rα2 is a very specific cell-surface target for glioma and is a suitable target for a CAR designed for treatment of a glioma.

[0029] Binding of IL13-based therapeutic molecules to the broadly expressed IL13Rα1/IL4β/γc receptor complex, however, has the potential of mediating undesired toxicities to normal tissues outside the CNS, and thus limits the systemic administration of these agents. An amino acid substitution in the IL13 alpha helix A at amino acid 13 of tyrosine for the native glutamic acid selectively reduces the affinity of IL13 to the IL13Rα1/IL4β/γc receptor. Binding of this mutant (termed IL13(E13Y)) to IL13Rα2, however, was increased relative to wild-type IL13. Thus, this minimally altered IL13 analog simultaneously increases IL13's specificity and affinity for glioma cells. Therefore, CAR described herein include an IL13 containing a mutation (E to Y or E to some other amino acid such as K or R or L or V) at amino acid 13 (according to the numbering of Debinski et al. 1999 Clin Cancer Res 5:3143s). IL13 having the natural sequence also may be used, however, and can be useful, particularly in situations where the modified T cells are to be locally administered, such as by injection directly into a tumor mass.

[0030] The CAR described herein can be produced by any means known in the art, though preferably it is produced using recombinant DNA techniques. Nucleic acids encoding the several regions of the chimeric receptor can be prepared and assembled into a complete coding sequence by standard techniques of molecular cloning known in the art (genomic

library screening, PCR, primer-assisted ligation, site-directed mutagenesis, etc.) as is convenient. The resulting coding region is preferably inserted into an expression vector and used to transform a suitable expression host cell line, preferably a T lymphocyte cell line, and most preferably an autologous T lymphocyte cell line.

[0031] Various T cell subsets isolated from the patient, including unselected PBMC or enriched CD3 T cells or enriched CD3 or memory T cell subsets, can be transduced with a vector for CAR expression. Central memory T cells are one useful T cell subset. Central memory T cell can be isolated from peripheral blood mononuclear cells (PBMC) by selecting for CD45RO+/CD62L+ cells, using, for example, the CliniMACS® device to immunomagnetically select cells expressing the desired receptors. The cells enriched for central memory T cells can be activated with anti-CD3/CD28, transduced with, for example, a SIN lentiviral vector that directs the expression of an IL13Rα2-specific CAR (e.g., IL13(EQ)BBζ+ as well as a truncated human CD19 (CD19t), a non-immunogenic surface marker for both in vivo detection and potential ex vivo selection. The activated/genetically modified central memory T cells can be expanded in vitro with IL-2/IL-15 and then cryopreserved.

Example 1: Construction and Structure of an IL13Rα2-specific CAR

[0032] The structure of a useful IL13Rα2-specific CAR is described below. The codon optimized CAR sequence contains a membrane-tethered IL-13 ligand mutated at a single site (E13Y) to reduce potential binding to IL13Rα1, an IgG4 Fc spacer containing two mutations (L235E; N297Q) that greatly reduce Fc receptor-mediated recognition models, a CD4 transmembrane domain, a costimulatory 4-1BB cytoplasmic signaling domain, and a CD3ζ cytoplasmic signaling domain. A T2A ribosome skip sequence separates this IL13(EQ)BBζ CAR sequence from CD19t, an inert, non-immunogenic cell surface detection/selection marker. This T2A linkage results in the coordinate expression of both IL13(EQ)BBζ and CD19t from a single transcript. **Figure 1A** is a schematic drawing of the 2670 nucleotide open reading frame encoding the IL13(EQ)BBZ-T2ACD19t construct. In this drawing, the IL13Rα2-specific ligand IL13(E13Y), IgG4(EQ) Fc, CD4 transmembrane, 4-1BB cytoplasmic signaling, three-glycine linker, and CD3ζ cytoplasmic signaling domains of the IL13(EQ)BBZ CAR, as well as the T2A ribosome skip and truncated CD19 sequences are all indicated. The human GM-CSF receptor alpha and CD19 signal sequences that drive surface expression of the IL13(EQ)BBZ CAR and CD19t are also indicated. Thus, the IL13(EQ)BBZ-T2ACD19t construct includes a IL13Rα2-specific, hinge-optimized, costimulatory chimeric immunoreceptor sequence (designated IL13(EQ)BBZ), a ribosome-skip T2A sequence, and a CD19t sequence.

[0033] The IL13(EQ)BBZ sequence was generated by fusion of the human GM-CSF receptor alpha leader peptide with IL13(E13Y) ligand 5 L235E/N297Q-modified IgG4 Fc hinge (where the double mutation interferes with FcR recognition), CD4 transmembrane, 4-1BB cytoplasmic signaling domain, and CD3ζ cytoplasmic signaling domain sequences. This sequence was synthesized de novo after codon optimization. The T2A sequence was obtained from digestion of a T2A-containing plasmid. The CD19t sequence was obtained from that spanning the leader peptide sequence to the transmembrane components (i.e., basepairs 1-972) of a CD19-containing plasmid. All three fragments, 1) IL13(EQ)BBZ, 2) T2A, and 3) CD19t, were cloned into the multiple cloning site of the epHIV7 lentiviral vector. When transfected into appropriate cells, the vector integrates the sequence depicted schematically in **Figure 1B** into the host cells genome. **Figure 1C** provides a schematic drawing of the 9515 basepair IL13(EQ)BBZ-T2A-CD19t_epHIV7 plasmid itself.

[0034] As shown schematically in **Figure 2**, IL13(EQ)BBZ CAR differs in several important respects from a previously described IL13Rα2-specific CAR referred to as IL13(E13Y)-zetakine (Brown et al. 2012 Clinical Cancer Research 18:2199). The IL13(E13Y)-zetakine is composed of the IL13Rα2-specific human IL-13 mutein (huIL-13(E13Y)), human IgG4 Fc spacer (huγ4Fc), human CD4 transmembrane (huCD4 tm), and human CD3ζ chain cytoplasmic (huCD3ζ cyt) portions as indicated. In contrast, the IL13(EQ)BBζ+ has two point mutations, L235E and N297Q that are located in the CH2 domain of the IgG4 spacer, and a costimulatory 4-1BB cytoplasmic domain (4-1BB cyt).

Example 2: Construction and Structure of epHIV7 used for Expression of an IL13Rα2-specific CAR

[0035] The pHIV7 plasmid is the parent plasmid from which the clinical vector IL13(EQ)BBZ-T2A-CD19t_epHIV7 was derived in the T cell Therapeutics Research Laboratory (TCTRL) at City of Hope (COH). The epHIV7 vector used for expression of the CAR was produced from pHIV7 vector. Importantly, this vector uses the human EF1 promoter to drive expression of the CAR. Both the 5' and 3' sequences of the vector were derived from pv653RSN as previously derived from the HXBc2 provirus. The polypurine tract DNA flap sequences (cPPT) were derived from HIV-1 strain pNL4-3 from the NIH AIDS Reagent Repository. The woodchuck post-transcriptional regulatory element (WPRE) sequence was previously described.

[0036] Construction of pHIV7 is schematically depicted in Figure 3. Briefly, pv653RSN, containing 653 bp from gag-pol plus 5' and 3' long-terminal repeats (LTRs) with an intervening SL3-neomycin phosphotransferase gene (Neo), was subcloned into pBluescript, as follows: In Step 1, the sequences from 5' LTR to rev-responsive element (RRE) made p5'HIV-1 51, and then the 5' LTR was modified by removing sequences upstream of the TATA box, and ligated first to

a CMV enhancer and then to the SV40 origin of replication (p5'HIV-2). In Step 2, after cloning the 3' LTR into pBluescript to make p3'HIV-1, a 400-bp deletion in the 3' LTR enhancer/promoter was made to remove cis-regulatory elements in HIV U3 and form p3'HIV-2. In Step 3, fragments isolated from the p5'HIV-3 and p3'HIV-2 were ligated to make pHIV-3. In Step 4, the p3'HIV-2 was further modified by removing extra upstream HIV sequences to generate p3'HIV-3 and a 600-bp BamHI-SalI fragment containing WPRE was added to p3'HIV-3 to make the p3'HIV-4. In Step 5, the pHIV-3 RRE was reduced in size by PCR and ligated to a 5' fragment from pHIV-3 (not shown) and to the p3'HIV-4, to make pHIV-6. In Step 6, a 190-bp BglII-BamHI fragment containing the cPPT DNA flap sequence from HIV-1 pNL4-3 (55) was amplified from pNL4-3 and placed between the RRE and the WPRE sequences in pHIV6 to make pHIV-7. This parent plasmid pHIV7-GFP (GFP, green fluorescent protein) was used to package the parent vector using a four-plasmid system.

[0037] A packaging signal, psi ψ, is required for efficient packaging of viral genome into the vector. The RRE and WPRE enhance the RNA transcript transport and expression of the transgene. The flap sequence, in combination with WPRE, has been demonstrated to enhance the transduction efficiency of lentiviral vector in mammalian cells.

[0038] The helper functions, required for production of the viral vector), are divided into three separate plasmids to reduce the probability of generation of replication competent lentivirus via recombination: 1) pCgp encodes the gag/pol protein required for viral vector assembly; 2) pCMV-Rev2 encodes the Rev protein, which acts on the RRE sequence to assist in the transportation of the viral genome for efficient packaging; and 3) pCMV-G encodes the glycoprotein of the vesiculo-stomatitis virus (VSV), which is required for infectivity of the viral vector.

[0039] There is minimal DNA sequence homology between the pHIV7 encoded vector genome and the helper plasmids. The regions of homology include a packaging signal region of approximately 600 nucleotides, located in the gag/pol sequence of the pCgp helper plasmid; a CMV promoter sequence in all three helper plasmids; and a RRE sequence in the helper plasmid pCgp. It is highly improbable that replication competent recombinant virus could be generated due to the homology in these regions, as it would require multiple recombination events. Additionally, any resulting recombinants would be missing the functional LTR and tat sequences required for lentiviral replication.

[0040] The CMV promoter was replaced by the EF1α-HTLV promoter (EF1p), and the new plasmid was named epHIV7 (**Figure 4**). The EF1p has 563 bp and was introduced into epHIV7 using NruI and NheI, after the CMV promoter was excised.

[0041] The lentiviral genome, excluding gag/pol and rev that are necessary for the pathogenicity of the wild-type virus and are required for productive infection of target cells, has been removed from this system. In addition, the IL13(EQ)BBZ-T2ACD19t_epHIV7 vector construct does not contain an intact 3'LTR promoter, so the resulting expressed and reverse transcribed DNA proviral genome in targeted cells will have inactive LTRs. As a result of this design, no HIV-I derived sequences will be transcribed from the provirus and only the therapeutic sequences will be expressed from their respective promoters. The removal of the LTR promoter activity in the SIN vector is expected to significantly reduce the possibility of unintentional activation of host genes (56). Table 4 summarizes the various regulator elements present in IL13(EQ)BBZ-T2ACD19t epHIV7.

Table 4 Functional elements of IL13(EQ)41BBZ-T2A-CD19t_epHIV7

Regulatory Elements and Genes	Location (Nucleotide Numbers)	Comments
U5	87-171	5' Unique sequence
psi	233-345	Packaging signal
RRE	957-1289	Rev-responsive element
flap	1290-1466	Contains polypurine track sequence and central termination sequence to facilitate nuclear import of pre-integration complex
FF1p Promoter	1524-2067	EF1-alpha Eukaryotic Promoter sequence driving expression of CD19Rop
IL13-IgG4 (EQ)-41BB-Zeta-T2A-CD19t	2084-4753	Therapeutic insert
WPRE	4790-5390	Woodchuck hepatitis virus derived regulatory element to enhance viral RNA transportation
delU3	5405-5509	3' U3 with deletion to generate SIN vector
R	5510-5590	Repeat sequence within LTR

(continued)

Table 4 Functional elements of IL13(EQ)41BBZ-T2A-CD19t_epHIV7		
Regulatory Elements and Genes	**Location (Nucleotide Numbers)**	**Comments**
U5	5591-5704	3' U5 sequence in LTR
Amp^R	6540-7398	Ampicillin-resistance gene
CoE1 ori	7461-8342	Replication origin of plasmid
SV40 ori	8639-8838	Replication origin of SV40
CMV promoter	8852-9451	CMV promoter to generate viral genome RNA
R	9507-86	Repeat sequence within LTR

Example 3: Production of Vectors for Transduction of Patient T Cells

[0042] For each plasmid (IL13(EQ)BBZ-T2A-CD19t_epHIV7; pCgp; pCMV-G; and pCMV-Rev2), a seed bank is generated, which is used to inoculate the fermenter to produce sufficient quantities of plasmid DNA. The plasmid DNA is tested for identity, sterility and endotoxin prior to its use in producing lentiviral vector.

[0043] Briefly, cells were expanded from the 293T working cell (WCB), which has been tested to confirm sterility and the absence of viral contamination. A vial of 293T cells from the 293T WCB was thawed. Cells were grown and expanded until sufficient numbers of cells existed to plate an appropriate number of 10 layer cell factories (CFs) for vector production and cell train maintenance. A single train of cells can be used for production.

[0044] The lentiviral vector was produced in sub-batches of up to 10 CFs. Two sub-batches can be produced in the same week leading to the production of approximately 20 L of lentiviral supernatant/week. The material produced from all sub-batches were pooled during the downstream processing phase, in order to produce one lot of product. 293T cells were plated in CFs in 293T medium (DMEM with 10% FBS). Factories were placed in a 37°C incubator and horizontally leveled in order to get an even distribution of the cells on all the layers of the CF. Two days later, cells were transfected with the four lentiviral plasmids described above using the CaPO4 method, which involves a mixture of Tris:EDTA, 2M CaCl2, 2X HBS, and the four DNA plasmids. Day 3 after transfection, the supernatant containing secreted lentiviral vectors was collected, purified and concentrated. After the supernatant was removed from the CFs, End-of-Production Cells were collected from each CF. Cells were trypsinized from each factory and collected by centrifugation. Cells were resuspended in freezing medium and cryopreserved. These cells were later used for replication-competent lentivirus (RCL) testing.

[0045] To purify and formulate vectors crude supernatant was clarified by membrane filtration to remove the cell debris. The host cell DNA and residual plasmid DNA were degraded by endonuclease digestion (Benzonase®). The viral supernatant was clarified of cellular debris using a 0.45 μm filter. The clarified supernatant was collected into a preweighed container into which the Benzonase® is added (final concentration 50 U/mL). The endonuclease digestion for residual plasmid DNA and host genomic DNA as performed at 37°C for 6 h. The initial tangential flow ultrafiltration (TFF) concentration of the endonuclease-treated supernatant was used to remove residual low molecular weight components from the crude supernatant, while concentrating the virus ~20 fold. The clarified endonuclease-treated viral supernatant was circulated through a hollow fiber cartridge with a NMWCO of 500 kD at a flow rate designed to maintain the shear rate at ~4,000 sec-1 or less, while maximizing the flux rate. Diafiltration of the nuclease-treated supernatant was initiated during the concentration process to sustain the cartridge performance. An 80% permeate replacement rate was established, using 4% lactose in PBS as the diafiltration buffer. The viral supernatant was brought to the target volume, representing a 20-fold concentration of the crude supernatant, and the diafiltration was continued for 4 additional exchange volumes, with the permeate replacement rate at 100%.

[0046] Further concentration of the viral product was accomplished by using a high speed centrifugation technique. Each sub-batch of the lentivirus was pelleted using a Sorvall RC-26 plus centrifuge at 6000 RPM (6,088 RCF) at 6oC for 16-20 h. The viral pellet from each sub-batch was then reconstituted in a 50 mL volume with 4% lactose in PBS. The reconstituted pellet in this buffer represents the final formulation for the virus preparation. The entire vector concentration process resulted in a 200-fold volume reduction, approximately. Following the completion of all of the sub-batches, the material was then placed at -80oC, while samples from each sub-batch were tested for sterility. Following confirmation of sample sterility, the sub-batches were rapidly thawed at 37oC with frequent agitation. The material was then pooled and manually aliquoted in the Class II Type A/B3 biosafety cabinet in the viral vector suite. A fill configuration of 1 mL

of the concentrated lentivirus in sterile USP class 6, externally threaded O-ring cryovials was used. Center for Applied Technology Development (CATD)'s Quality Systems (QS) at COH released all materials according to the Policies and Standard Operating Procedures for the CBG and in compliance with current Good Manufacturing Practices (cGMPs).

[0047] To ensure the purity of the lentiviral vector preparation, it was tested for residual host DNA contaminants, and the transfer of residual host and plasmid DNA. Among other tests, vector identity was evaluated by RT-PCR to ensure that the correct vector is present. All release criteria were met for the vector intended for use in this study.

Example 4: Preparation of T cells Suitable for Use in ACT

[0048] T lymphocytes are obtained from a patient by leukopheresis, and the appropriate allogenic or autologous T cell subset, for example, Central Memory T cells (T_{CM}), are genetically altered to express the CAR, then administered back to the patient by any clinically acceptable means, to achieve anti-cancer therapy.

[0049] An outline of the manufacturing strategy for T_{CM} is depicted in **Figure 8** (Manufacturing schema for IL13(EQ)BBζ/CD19t+ T_{CM}). Specifically, apheresis products obtained from consented research participants are ficolled, washed and incubated overnight. Cells are then depleted of monocyte, regulatory T cell and naive T cell populations using GMP grade anti-CD14, anti-CD25 and anti-CD45RA reagents (Miltenyi Biotec) and the CliniMACS™ separation device. Following depletion, negative fraction cells are enriched for CD62L+ T_{CM} cells using DREG56-biotin (COH clinical grade) and anti-biotin microbeads (Miltenyi Biotec) on the CliniMACSTM separation device.

[0050] Following enrichment, T_{CM} cells are formulated in complete X-Vivo15 plus 50 IU/mL IL-2 and 0.5 ng/mL IL-15 and transferred to a Teflon cell culture bag, where they are stimulated with Dynal ClinEx™ Vivo CD3/CD28 beads. Up to five days after stimulation, cells are transduced with IL13(EQ)BBZ-T2A-CD19t_epHIV7 lentiviral vector at a multiplicity of infection (MOI) of 1.0 to 0.3. Cultures are maintained for up to 42 days with addition of complete X-Vivo15 and IL-2 and IL-15 cytokine as required for cell expansion (keeping cell density between $3x10^5$ and $2x10^6$ viable cells/mL, and cytokine supplementation every Monday, Wednesday and Friday of culture). Cells typically expand to approximately 10^9 cells under these conditions within 21 days. At the end of the culture period cells are harvested, washed twice and formulated in clinical grade cryopreservation medium (Cryostore CS5, BioLife Solutions).

[0051] On the day(s) of T cell infusion, the cryopreserved and released product is thawed, washed and formulated for re-infusion. The cryopreserved vials containing the released cell product are removed from liquid nitrogen storage, thawed, cooled and washed with a PBS/2% human serum albumin (HSA) Wash Buffer. After centrifugation, the supernatant is removed and the cells resuspended in a Preservative-Free Normal Saline (PFNS)/ 2% HSA infusion diluent. Samples are removed for quality control testing.

[0052] Two qualification runs on cells procured from healthy donors were performed using the manufacturing platform described above. Each preclinical qualification run product was assigned a human donor (HD) number - HD006.5 and HD187.1. Importantly, as shown in Table 5, these qualification runs expanded >80 fold within 28 days and the expanded cells expressed the IL13(EQ)BBγ/CD19t transgenes.

Table 5: Summary of Expression Data from Pre-clinical Qualification Run Product

Cell Product	CAR	CD19	CD4+	CD8+	Fold Expansion
HD006.5	20%	22%	24%	76%	84-fold (28 days)
Hd187.1	18%	25%	37%	63%	259-fold (28 days)

Example 5: Flow cytometric analysis of surface transgene and T cell marker expression in IL13(EQ)BBγ/CD19t+T_{CM}

[0053] The two preclinical qualification run products described in Example 4 were used in pre-clinical studies to as described below. **Figures 6A-C** depict the results of flow cytometric analysis of surface transgene and T cell marker expression. IL13(EQ)BBγ/CD19t+ T_{CM} HD006.5 and HD187.1 were co-stained with anti-IL13-PE and anti-CD8-FITC to detect CD8+ CAR+ and CD4+ (i.e., CD8 negative) CAR+ cells (**Figure 6A**), or anti-CD 19-PE and anti-CD4-FITC to detect CD4+ CD19t+ and CD8+ (i.e., CD4 negative) CAR+ cells (**Figure 6B**). IL13(EQ)BBγ/CD19t+ T_{CM} HD006.5 and HD187.1 were stained with fluorochrome-conjugated anti-CD3, TCR, CD4, CD8, CD62L and CD28 (grey histograms) or isotype controls (black histograms). (**Figure 6C**). In each of **Figures 6A-C**, the percentages indicated are based on viable lymphocytes (DAPI negative) stained above isotype.

Example 6: Effector Activity of IL 13(EQ)BBγ/CD19t+ T_{CM}

[0054] The effector activity of IL13(EQ)BBζ/CD19t+ T_{CM} was assessed and the results of this analysis are depicted in **Figures 7A-B**. Briefly, IL13(EQ)BBγ/CD19t+ T_{CM} HD006.5 and HD187.1 were used as effectors in a 6-hour 51Cr-

release assay using a 10E:1T ratio based on CD19t expression. The IL13Rα2-positive tumor targets were K562 engineered to express IL13Rα2 (K562-IL13Rα2) and primary glioma line PBT030-2, and the IL13Rα2-negative tumor target control was the K562 parental line (**Figure 7A**). IL13(EQ)BBγ/CD19t+ HD006.5 and HD187.1 were evaluated for antigen-dependent cytokine production following overnight co-culture at a 10E:1T ratio with the same IL13Rα2-positive and negative targets as described in above. Cytokine levels were measured using the Bio-Plex Pro Human Cytokine TH1/TH2 Assay kit and INF-γ levels are depicted (**Figure 7B**).

Example 7: *In vivo* Anti-tumor Activity of IL13(EQ)BBγ/CD19t+ T_{CM}

[0055] The studies described below demonstrate that IL13(EQ)BBγ/CD19t+ T_{CM} exhibit anti-tumor efficacy in *in vivo* mouse models. Specifically, we have evaluated the anti-tumor potency of IL13(EQ)BBγ/CD19t+ T_{CM} against the IL13Rα2+ primary low-passage glioblastoma tumor sphere line PBT030-2, which has been engineered to express both EGFP and firefly luciferase (ffLuc) reporter genes (PBT030-2 EGFP:ffLuc) (**6**). A panel of primary lines (PBT) from patient glioblastoma specimens grown as tumor spheres (TSs) in serum-free media. These expanded TS lines exhibit stem cell-like characteristics, including expression of stem cell markers, multilineage differentiation and capacity to initiate orthotopic tumors in immunocompromised mice (NSG) at low cell numbers. The PBT030-2 EGFP:ffLuc TS-initiated xenograft model ($0.1x10^6$ cells; 5 day engraftment) has been previously used to evaluate in vivo anti-tumor activity in NSG mice of IL13Rα2-specific CAR expressing T cells, whereby three injections of $2x10^6$ cytolytic T lymphocytes (CTLs) over a course of 2 weeks were shown to reduce tumor growth. However, in those experiments the majority of the PBT030-2 tumors eventually recurred. By comparison, a single injection of IL13(EQ)BBγ/CD19t+ T_{CM} ($1.1x10^6$ CAR+ T_{CM}; $2x10^6$ total TCM) exhibited robust anti-tumor activity against PBT030-2 EGFP:ffLuc TS-initiated tumors ($0.1x10^6$ cells; 5 day engraftment) as shown in **Figures 8A-C**. As compared to NSG mice treated with either PBS or mock transduced T_{CM} (no CAR), IL13(EQ)BBγ/CD19t+ T_{CM} significantly reduce ffLuc flux ($p < 0.001$ at >18-days) and significantly improve survival ($p = 0.0008$).

[0056] Briefly, EGFP-ffLuc+ PBT030-2 tumor cells (1×10^5) were stereotactically implanted into the right forebrain of NSG mice. On day 5, mice received either $2x10^6$ IL13(EQ)BBγ/CDI9t+ T_{CM} (1.1x106 CAR+; n=6), $2x10^6$ mock T_{CM} (no CAR; n=6) or PBS (n=6). **Figure 8A** depicts representative mice from each group showing relative tumor burden using Xenogen Living Image. Quantification of ffLuc flux (photons/sec) shows that IL13(EQ)BBζ/CD19t+ T_{CM} induce tumor regression as compared to mock-transduced T_{CM} and PBS (#p<0.02, *p<0.001, repeated measures ANOVA) (**Figure 8B**). As shown in **Figure 8C**, a Kaplan Meier survival curve (n=6 per group) demonstrates significantly improved survival (p=0.0008; log-rank test) for mice treated with IL13(EQ)BBγ/CD19t+ T_{CM}.

Example 8: Comparison of IL13(EQ)BBζ+ Tcm and Non-Tcm IL13-zetakine CD8+ CTL Clones in Antitumor Efficacy and T cell Persistence

[0057] The studies described below compare IL13(EQ)BBζ+ Tcm and a previously created IL13Rα2-specific human CD8+ CTLs (IL13-zetakine CD8+ CTL (described in Brown et al. 2012 Clin Cancer Res 18:2199 and Kahlon et al. 2004 Cancer Res 64:9160). The IL13-zetakine uses a CD3ζ stimulatory domain, lacks a co-stimulatory domain and uses the same IL13 variant as IL13(EQ)BBζ+.

[0058] A panel of primary lines (PBT) from patient glioblastoma specimens grown as tumor spheres (TSs) in serum-free media was generated (Brown et al. 2012 Clin Cancer Res 18:2199; Brown et al. 2009 Cancer Res 69:8886). These expanded TS lines exhibit stem cell-like characteristics, including expression of stem cell markers, multi-lineage differentiation and capacity to initiate orthotopic tumors in immunocompromised mice (NSG) at low cell numbers. The IL13Rα2+ primary low-passage glioblastoma TS line PBT030-2, which has been engineered to express both EGFP and firefly luciferase (ffLuc) reporter genes (PBT030-2 EGFP:ffLuc) (Brown et al. 2012 Clin Cancer Res 18:2199) was used for the experiments outlined below.

[0059] First, a single dose ($1x10^6$ CAR T cells) of IL13(EQ)BBζ+ Tcm product was compared to IL13-zetakine CD8+ CTL clones evaluated against day 8 PBT030-2 EGFP:ffuc TS-initiated xenografts ($0.1x10^6$ cells). While both IL13Rα2-specific CAR T cells (IL13-zetakine CTL and IL13(EQ)BBζ Tcm) demonstrated antitumor activity against established PBT030-2 tumors as compared to untreated and mock Tcm (CAR-negative) controls (**Figures 9A** and **9B**), IL13(EQ)BBZ+ Tcm mediated significantly improved survival and durable tumor remission with mice living >150 days as compared to our first-generation IL13-zetakine CD8+ CTL clones (**Figure 9C**).

[0060] To further compare the therapeutic effectiveness of these two IL13Rα2-CAR T cell products, a dose titration of 1.0, 0.3 and $0.1x10^6$ CAR T cells against day 8 PBT030-2 EGFP:ffuc TS-initiated tumors was performed (**Figures 10A-C**). The highest dose ($1x10^6$) of IL13-zetakine CD8+ CTL cl. 2D7 mediated antitumor responses as measured by Xenogen flux in 3 of 6 animals (**Figure 10C**), but no significant antitumor responses were observed at lower CAR T cell doses. By comparison, injection of IL13(EQ)BBζ+ Tcm product mediated complete tumor regression in the majority of mice at all dose levels, including treatment with as few as $0.1x10^6$ CAR T cells. These data demonstrate that

IL13(EQ)BBζ+ Tcm is at least 10-fold more potent than IL13-zetakine CD8+ CTL clones in antitumor efficacy. The improved anti-tumor efficacy of is due to improved T cell persistence in the tumor microenvironment. Evaluation of CD3+ T cells 7-days post i.c. injection revealed significant numbers of IL13(EQ)BBζ+ Tcm in the tumor microenvironment, whereas very few first-generation IL13-zeta CTLs were present (**Figure 11**).

Example 9: Comparison of CAR T cell delivery route for treatment of large TS-initiated PBT tumors

[0061] Described below are studies that compare the route of delivery, intraveneous (i.v.) or intracranial (i.c.), on antitumor activity against invasive primary PBT lines. In pilot studies (data not shown), it was unexpectedly observed that i.v. administered IL13(EQ)BBζ+ Tcm provided no therapeutic benefit as compared to PBS for the treatment of small (day 5) PBT030-2 EGFP:ffLuc tumors. This is in contrast to the robust therapeutic efficacy observed with i.c. administered CAR+ T cells. Reasoning that day 5 PBT030-2 tumors may have been too small to recruit therapeutic T cells from the periphery, a comparison was made of i.v. versus i.c. delivery against larger day 19 PBT030-2 EGFP:ffLuc tumors. For these studies, PBT030-2 engrafted mice were treated with either two i.v. infusions (5 x 10^6 CAR+ Tcm; days 19 and 26) or four i.c. infusions (1 x 10^6 CAR+ Tcm; days 19, 22, 26 and 29) of IL13(EQ)BBZ+ Tcm, or mock Tcm (no CAR). Here too no therapeutic benefit as monitored by Xenogen imaging or Kaplan-Meier survival analysis for i.v. administered CAR+ T cells (**Figures 12A** and **12B**). In contrast, potent antitumor activity was observed for i.c. administered IL13(EQ)BBζ+ Tcm (**Figures 12A-B**). Next, brains from a cohort of mice 7 days post T cell injection were harvested and evaluated for CD3+ human T cells by IHC. Surprisingly, for mice treated i.v. with either mock Tcm or IL13(EQ)BBζ Tcm there were no detectable CD3+ human T cells in the tumor or in others mouse brain regions where human T cells typically reside (i.e. the leptomeninges) (**Figure 12C**), suggesting a deficit in tumor tropism. This is in contrast to the significant number of T cells detected in the i.c. treated mice (**Figure 12D**).

[0062] Tumor derived cytokines, particularly MCP-1/CCL2, are important in recruiting T cells to the tumor. Thus, PBT030-2 tumor cells were evaluated and it was found that this line produces high levels of MCP-1/CCL2 comparable to U251T cells (data not shown), a glioma line previously shown to attract i.v. administered effector CD8+ T cells to i.c. engrafted tumors. Malignant gliomas are highly invasive tumors and are often multifocal in presentation. The studies described above establish that IL13BBZ T_{CM} can eliminate infiltrated tumors such as PBT030-2, and mediate long-term durable antitumor activity. The capacity of intracranially delivered CAR T cells to traffic to multifocal disease was also examined. For this study PBT030-2 EGFP:ffLuc TSs were implanted in both the left and right hemispheres (**Figure 13A**) and CAR+ T cells were injected only at the right tumor site. Encouragingly, for all mice evaluated (n=3) we detected T cells by CD3 IHC 7-days post T cell infusion both at the site of injection (i.e. right tumor), as well within the tumor on the left hemisphere (**Figure 13B**). These findings provide evidence that CAR+ T cells are able to traffic to and infiltrate tumor foci at distant sites. Similar findings were also observed in a second tumor model using the U251T glioma cell line (data not shown).

Example 10: Comparison of Costimulatory Domains

[0063] A series of studies were conducted to evaluate various costimulatory domains. The various CAR evaluated are depicted schematically in **Figure 14A** and included a first generation CD3ζ CAR lacking a costimulatory domain, two second generation CARs incorporating either a 4-1BB costimulatory domain or a CD28 costimulatory domain, and a third generation CAR containing both a CD28 costimulatory domain and 41BB costimulatory domain. All CAR constructs also contain the T2A ribosomal skip sequence and a truncated CD19 (CD19t) sequence as a marker for transduced cells.

[0064] CD4 and CD8 T_{CM} were lentivirally transduced and CAR-expressing T cells were immunomagnetically enriched via anti-CD19. CD19 and IL13 (i.e., CAR) expression levels as measured by flow cytometry. The results are shown in **Figure 14B**. Stability of each CAR construct was determined by dividing the CAR (IL13) mean flourescence intenstity (MFI) by that of the transduction marker (CD19t) (**Figure 14C**). The two CAR including a 4-1BB costimulatory domain exhibited the lowest expression levels as compared to the CD19t transduction marker.

[0065] The ability of the indicated mock-transduced or CAR-expressing T cells to kill IL13Rα2-expressing PBT030-2 tumor cell targets was determined in a 4-hour ^{51}Cr-release assay at the indicated effector:target ratios. The results of this study are in **Figure 15A** (mean % chromium release + S.D. of triplicate wells are depicted). As expected, mock-transduced T cells did not efficiently lyse the targets. In contrast, all CAR-expressing T cells lysed the tumor cells in a similar manner. **Figure 15B** depicts the results of a study in which the indicated mock-transduced or CAR-expressing T cells were co-cultured overnight with IL13Rα2-expressing PBT030-2 tumor cells at a 10:1 ratio and supernatants were analyzed for IL-13 and IFN-γ levels by cytometric bead array. Interestingly, T cells expressing the zeta, 41BB-zeta or CD28-41BB-zeta CARs exhibited lower antigen-stimulated cytokine production than T cells expressing the CD28-zeta CAR.

[0066] The in vivo efficacy of the various CAR was examined as follows. Briefly, NSG mice received an intracranial injection of ffLuc+ PBT030-2 tumor cells on day 0, and were randomized into 6 groups (n = 9-10 mice per group) for i.c.

treatment with either PBS (Tumor Only), mock-transduced T cells or T cells expressing the indicated IL13Rα2-specific CAR on day 8. Quantitative bioluminescence imaging was then carried out to monitor tumor growth over time. Bioluminescence images for representative mice in each group (**Figure 16A**). Flux levels for each mouse at Day 27 (**Figure 16B**). All groups treated with IL13Rα2-specific CAR T cells, except those treated with T cells expressing the CD28-CAR, show statistically-significant reduction in tumor volume compared to mice treated with mock-transduced T cells (**Figure 16C**).

Example 11: Amino acid Sequence of IL13(EQ)BBζ/CD19t

[0067] The complete amino acid sequence of IL13(EQ)BBζ/CD19t is depicted in **Figure 17**. The entire sequence (SEQ ID NO:1) includes: a 22 amino acid GMCSF signal peptide (SEQ ID NO:2), a 112 amino acid IL-13 sequence (SEQ ID NO:3; amino acid substitution E13Y shown in bold); a 229 amino acid IgG4 sequence (SEQ ID NO:4; with amino acid substitutions L235E and N297Q shown in bold); a 22 amino acid CD4 transmembrane sequence (SEQ ID NO:5); a 42 amino acid 4-1BB sequence (SEQ ID NO:6); a 3 amino acid Gly linker; a 112 amino acid CD3ζ sequence (SEQ ID NO:7); a 24 amino acid T2A sequence (SEQ ID NO:8); and a 323 amino acid CD19t sequence (SEQ ID NO:9).
[0068] The mature chimeric antigen receptor sequence (SEQ ID NO:10) includes: a 112 amino acid IL-13 sequence (SEQ ID NO:3; amino acid substitution E13Y shown in bold); a 229 amino acid IgG4 sequence (SEQ ID NO:4; with amino acid substitutions L235E and N297Q shown in bold); at 22 amino acid CD4 sequence (SEQ ID NO:5); a 42 amino acid 4-1BB sequence (SEQ ID NO:6); a 3 amino acid Gly linker; and a 112 amino acid CD3ζ sequence (SEQ ID NO:7). Within this CAR sequence (SEQ ID NO:10) is the IL-13/IgG4/CD4t/41-BB sequence (SEQ ID NO:11), which includes: a 112 amino acid IL-13 sequence (SEQ ID NO:3; amino acid substitution E13Y shown in bold); a 229 amino acid IgG4 sequence (SEQ ID NO:4; with amino acid substitutions L235E and N297Q shown in bold); at 22 amino acid CD4 sequence (SEQ ID NO:5); and a 42 amino acid 4-1BB sequence (SEQ ID NO:6). The IL13/IgG4/CD4t/4-1BB sequence (SEQ ID NO:11) can be joined to the 112 amino acid CD3ζ sequence (SEQ ID NO:7) by a linker such as a Gly Gly Gly linker. The CAR sequence (SEQ ID NO:10) can be preceded by a 22 amino acid GMCSF signal peptide (SEQ ID NO:2).
[0069] **Figure 18** depicts a comparison of the sequences of IL13(EQ)41BBζ[IL13{EQ}41BBζ T2A-CD19t_epHIV7; pF02630] (SEQ ID NO:12) and CD19Rop_epHIV7 (pJ01683) (SEQ ID NO:13).

Example 12: Amino acid Sequence of IL13(EQ)BBζ/CD19t

[0070] **Figures 19-26** depict the amino acid sequences of additional CAR directed against IL13Rα2 in each case the various domains are labelled except for the GlyGlyGly spacer located between certain intracellular domains. Each includes human IL13 with and Glu to Tyr (SEQ ID NO:3; amino acid substitution E13Y shown in highlighted). In the expression vector used to express these CAR, the amino acid sequence expressed can include a 24 amino acid T2A sequence (SEQ ID NO:8); and a 323 amino acid CD19t sequence (SEQ ID NO:9) to permit coordinated expression of a truncated CD19 sequence on the surface of CAR-expressing cells.
[0071] A panel of CAR comprising human IL13(E13Y) domain, a CD28 tm domain, a CD28gg costimulatory domain, a 4-1BB costimulatory domain, and a CD3ζ domain CAR backbone and including either a HL (22 amino acids) spacer, a CD8 hinge (48 amino acids) spacer, IgG4-HL-CH3 (129 amino acids) spacer or a IgG4(EQ) (229 amino acids) spacer were tested for their ability to mediate IL13Ra2-specific killing as evaluated in a 72-hour co-culture assay. With the exception of HL (22 amino acids) which appeared to have poor CAR expression in this system, all were active.

EMBODIMENTS

[0072] Although the present invention is defined in the attached claims, it should be understood that the present invention can also (alternatively) be defined in accordance with the following embodiments:

1. A nucleic acid molecule encoding a chimeric antigen receptor, wherein the chimeric antigen receptor comprises: human IL-13 or a variant thereof having 1-10 amino acid modifications; a transmembrane domain selected from: a CD4 transmembrane domain or variant thereof having 1-10 amino acid modifications, a CD8 transmembrane domain or variant thereof having 1-10 amino acid modifications, a CD28 transmembrane domain or a variant thereof having 1-10 amino acid modifications, and a CD3ζ transmembrane domain or a variant thereof having 1-10 amino acid modifications; a costimulatory domain; and CD3 ζ signaling domain of a variant thereof having 1-10 amino acid modifications.

2. The nucleic acid molecule of embodiment 1 wherein the costimulatory domain is selected from the group consisting of: a CD28 costimulatory domain or a variant thereof having 1-10 amino acid modifications, a 4IBB costimulatory

domain or a variant thereof having 1-10 amino acid modifications and an OX40 costimulatory domain or a variant thereof having 1-10 amino acid modifications.

3. The nucleic acid molecule of embodiment 1 comprising a variant of a human IL13 having 1-10 amino acid modification that increase binding specificity for IL13Rα2 versus IL13Rα1.

4. The nucleic acid molecule of embodiment 1 wherein the human IL-13 or variant thereof is an IL-13 variant comprising the amino acid sequence of SEQ ID NO:3 with 1 to 5 amino acid modifications, provided that the amino acid at position 11 of SEQ ID NO:3 other than E.

5. The nucleic acid molecule of embodiment 2 wherein the chimeric antigen receptor comprises two different costimulatory domains selected from the group consisting of: a CD28 costimulatory domain or a variant thereof having 1-10 amino acid modifications, a 4IBB costimulatory domain or a variant thereof having 1-10 amino acid modifications and an OX40 costimulatory domain or a variant thereof having 1-10 amino acid modifications.

6. The nucleic acid molecule of embodiment 5 wherein the chimeric antigen receptor comprises two different costimulatory domains selected from the group consisting of: a CD28 costimulatory domain or a variant thereof having 1-2 amino acid modifications, a 4IBB costimulatory domain or a variant thereof having 1-2 amino acid modifications and an OX40 costimulatory domain or a variant thereof having 1-2 amino acid modifications.

7. The nucleic acid molecule of embodiment 1 wherein the chimeric antigen receptor comprises: human IL-13 or a variant thereof having 1-2 amino acid modifications; a transmembrane domain selected from: a CD4 transmembrane domain or variant thereof having 1-2 amino acid modifications, a CD8 transmembrane domain or variant thereof having 1-2 amino acid modifications, a CD28 transmembrane domain or a variant thereof having 1-2 amino acid modifications, and a CD3ζ transmembrane domain or a variant thereof having 1-2 amino acid modifications; a costimulatory domain; and CD3 ζ signaling domain of a variant thereof having 1-2 amino acid modifications.

8. The nucleic acid molecule of embodiment 1 comprising a spacer region located between the IL-13 or variant thereof and the transmembrane domain.

9. The nucleic acid molecule of embodiment 6 wherein the spacer region comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 14-20, 50 and 521.

10. The nucleic acid molecule of embodiment 6 wherein the spacer comprises an IgG hinge region.

11. The nucleic acid molecule of embodiment 6 wherein the spacer comprises 10-150 amino acids.

12. The nucleic acid molecule of embodiment 2 wherein the 4-1BB signaling domain comprises the amino acid sequence of SEQ ID NO:6.

13. The nucleic acid molecule of embodiment 1 wherein the CD3ζ signaling domain comprises the amino acid sequence of SEQ ID NO:7.

14. The nucleic acid molecule of embodiment 1 wherein a linker of 3 to 15 amino acids is located between the costimulatory domain and the CD3 ζ signaling domain or variant thereof.

15. The nucleic acid molecule of embodiment 1 wherein the nucleic acid molecule expresses a polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 10, 31-48 and 52.

16. The nucleic acid molecule of embodiment 1 wherein the chimeric antigen receptor comprises a IL-13/IgG4/CD4t/41-BB region comprising the amino acid of SEQ ID NO:11 and a CD3 ζ signaling domain comprising the amino acid sequence of SEQ ID NO:7.

17. The nucleic acid molecule of embodiment 14 wherein the chimeric antigen receptor comprises the amino acid sequence of SEQ ID NOs: 10, 31-48 and 52.

18. A population of human T cells transduced by a vector comprising an expression cassette encoding a chimeric antigen receptor, wherein chimeric antigen receptor comprises: human IL-13 or a variant thereof having 1-10 amino

acid modifications; a transmembrane domain selected from: a CD4 transmembrane domain or variant thereof having 1-10 amino acid modifications, a CD8 transmembrane domain or variant thereof having 1-10 amino acid modifications, a CD28 transmembrane domain or a variant thereof having 1-10 amino acid modifications, and a CD3ζ transmembrane domain or a variant thereof having 1-10 amino acid modifications; a costimulatory domain; and CD3 ζ signaling domain of a variant thereof having 1-10 amino acid modifications.

19. A population of human T cells comprising a vector expressing a chimeric antigen receptor comprising an amino acid sequence selected from SEQ ID NOs: 10, 31-48 and 52.

20. The population of human T cells of embodiment 16 wherein the T cells are comprised of a population of central memory T cells.

21. A method of treating cancer in a patient comprising administering a population of autologous or allogeneic human T cells transduced by a vector comprising an expression cassette encoding a chimeric antigen receptor, wherein chimeric antigen receptor comprises an amino acid sequence selected from SEQ ID NOs: 10, 31-48 and 52.

22. The method of embodiment 19 wherein the population of human T cells comprise central memory T cells.

23. The method embodiment 19 wherein the cancer is glioblastoma.

24. The method of embodiment 20 wherein the transduced human T cells where prepared by a method comprising obtaining T cells from the patient, treating the T cells to isolate central memory T cells, and transducing at least a portion of the central memory cells to with a viral vector comprising an expression cassette encoding a chimeric antigen receptor, wherein chimeric antigen receptor comprises an amino acid sequence selected from SEQ ID NOs: 10, 31-48 and 52.

25. A nucleic acid molecule encoding an polypeptide comprising an amino acid sequence that is at least 95% identical to an amino acid sequence selected from SEQ ID NO:10 and SEQ ID NOs: 10, 31-48 and 52.

26. A nucleic acid molecule encoding an polypeptide comprising an amino acid sequence that is identical to an amino acid sequence selected from SEQ ID NO: 10, 31-48 and 52 except for the presence of no more than 5 amino acid substitutions, deletions or insertions.

27. A nucleic acid molecule encoding an polypeptide comprising an amino acid sequence that is identical to an amino acid sequence selected from SEQ ID NO:10 and SEQ ID NOs: 10, 31-48 and 52 except for the presence of no more than 5 amino acid substitutions.

28. A nucleic acid molecule encoding an polypeptide comprising an amino acid sequence that is identical to an amino acid sequence selected from SEQ ID NO:10 and SEQ ID NOs: 10, 31-48 and 52 except for the presence of no more than 2 amino acid substitutions.

SEQUENCE LISTING

<110> CITY OF HOPE

<120> COSTIMULATORY CHIMERIC ANTIGEN RECEPTOR T CELLS TARGETING IL13R-ALPHA-2

<130> 40056-0002EP1

<150> 62/053,068
<151> 2014-09-19

<160> 54

<170> PatentIn version 3.5

<210> 1
<211> 889
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1

```
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                  10                  15

Ala Phe Leu Leu Ile Pro Gly Pro Val Pro Pro Ser Thr Ala Leu Arg
            20                  25                  30

Tyr Leu Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro
        35                  40                  45

Leu Cys Asn Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met
    50                  55                  60

Tyr Cys Ala Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala
65                  70                  75                  80

Ile Glu Lys Thr Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val
                85                  90                  95

Ser Ala Gly Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu
            100                 105                 110

Val Ala Gln Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe
        115                 120                 125

Arg Glu Gly Arg Phe Asn Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
    130                 135                 140
```

```
Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro
145                 150                 155                 160

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
                165                 170                 175

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
            180                 185                 190

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
        195                 200                 205

Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
    210                 215                 220

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
225                 230                 235                 240

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
                245                 250                 255

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
            260                 265                 270

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
        275                 280                 285

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
    290                 295                 300

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
305                 310                 315                 320

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
                325                 330                 335

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
            340                 345                 350

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Ala Leu Ile Val
        355                 360                 365

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
    370                 375                 380

Phe Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
385                 390                 395                 400
```

```
Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
                405                 410                 415

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val
            420                 425                 430

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
        435                 440                 445

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
    450                 455                 460

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
465                 470                 475                 480

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
                485                 490                 495

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
            500                 505                 510

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
        515                 520                 525

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Leu Glu
    530                 535                 540

Gly Gly Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu
545                 550                 555                 560

Glu Asn Pro Gly Pro Arg Met Pro Pro Pro Arg Leu Leu Phe Phe Leu
                565                 570                 575

Leu Phe Leu Thr Pro Met Glu Val Arg Pro Glu Glu Pro Leu Val Val
            580                 585                 590

Lys Val Glu Glu Gly Asp Asn Ala Val Leu Gln Cys Leu Lys Gly Thr
        595                 600                 605

Ser Asp Gly Pro Thr Gln Gln Leu Thr Trp Ser Arg Glu Ser Pro Leu
    610                 615                 620

Lys Pro Phe Leu Lys Leu Ser Leu Gly Leu Pro Gly Leu Gly Ile His
625                 630                 635                 640

Met Arg Pro Leu Ala Ile Trp Leu Phe Ile Phe Asn Val Ser Gln Gln
```

645 650 655

Met Gly Gly Phe Tyr Leu Cys Gln Pro Gly Pro Pro Ser Glu Lys Ala
660 665 670

Trp Gln Pro Gly Trp Thr Val Asn Val Glu Gly Ser Gly Glu Leu Phe
675 680 685

Arg Trp Asn Val Ser Asp Leu Gly Gly Leu Gly Cys Gly Leu Lys Asn
690 695 700

Arg Ser Ser Glu Gly Pro Ser Ser Pro Ser Gly Lys Leu Met Ser Pro
705 710 715 720

Lys Leu Tyr Val Trp Ala Lys Asp Arg Pro Glu Ile Trp Glu Gly Glu
725 730 735

Pro Pro Cys Val Pro Pro Arg Asp Ser Leu Asn Gln Ser Leu Ser Gln
740 745 750

Asp Leu Thr Met Ala Pro Gly Ser Thr Leu Trp Leu Ser Cys Gly Val
755 760 765

Pro Pro Asp Ser Val Ser Arg Gly Pro Leu Ser Trp Thr His Val His
770 775 780

Pro Lys Gly Pro Lys Ser Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg
785 790 795 800

Pro Ala Arg Asp Met Trp Val Met Glu Thr Gly Leu Leu Leu Pro Arg
805 810 815

Ala Thr Ala Gln Asp Ala Gly Lys Tyr Tyr Cys His Arg Gly Asn Leu
820 825 830

Thr Met Ser Phe His Leu Glu Ile Thr Ala Arg Pro Val Leu Trp His
835 840 845

Trp Leu Leu Arg Thr Gly Gly Trp Lys Val Ser Ala Val Thr Leu Ala
850 855 860

Tyr Leu Ile Phe Cys Leu Cys Ser Leu Val Gly Ile Leu His Leu Gln
865 870 875 880

Arg Ala Leu Val Leu Arg Arg Lys Arg
885

<210> 2
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 2
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro
20

<210> 3
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 3
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1 5 10 15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
20 25 30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
35 40 45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
50 55 60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65 70 75 80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
85 90 95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
100 105 110

<210> 4
<211> 229
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 4

```
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                  10                  15

Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145                 150                 155                 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Lys
```

225

<210> 5
<211> 22
<212> PRT
<213> Homo sapiens

<400> 5
Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile
1 5 10 15

Gly Leu Gly Ile Phe Phe
20

<210> 6
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 6
Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1 5 10 15

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
20 25 30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
35 40

<210> 7
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
100 105 110

<210> 8
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 8
Leu Glu Gly Gly Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp
1 5 10 15

Val Glu Glu Asn Pro Gly Pro Arg
20

<210> 9
<211> 323
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 9
Met Pro Pro Pro Arg Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met
1 5 10 15

Glu Val Arg Pro Glu Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp
20 25 30

Asn Ala Val Leu Gln Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln
35 40 45

Gln Leu Thr Trp Ser Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu
50 55 60

Ser Leu Gly Leu Pro Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile

65 70 75 80

Trp Leu Phe Ile Phe Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu
85 90 95

Cys Gln Pro Gly Pro Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr
100 105 110

Val Asn Val Glu Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp
115 120 125

Leu Gly Gly Leu Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro
130 135 140

Ser Ser Pro Ser Gly Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala
145 150 155 160

Lys Asp Arg Pro Glu Ile Trp Glu Gly Glu Pro Pro Cys Val Pro Pro
165 170 175

Arg Asp Ser Leu Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro
180 185 190

Gly Ser Thr Leu Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser
195 200 205

Arg Gly Pro Leu Ser Trp Thr His Val His Pro Lys Gly Pro Lys Ser
210 215 220

Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg Pro Ala Arg Asp Met Trp
225 230 235 240

Val Met Glu Thr Gly Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala
245 250 255

Gly Lys Tyr Tyr Cys His Arg Gly Asn Leu Thr Met Ser Phe His Leu
260 265 270

Glu Ile Thr Ala Arg Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly
275 280 285

Gly Trp Lys Val Ser Ala Val Thr Leu Ala Tyr Leu Ile Phe Cys Leu
290 295 300

Cys Ser Leu Val Gly Ile Leu His Leu Gln Arg Ala Leu Val Leu Arg
305 310 315 320

Arg Lys Arg

<210> 10
<211> 520
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 10

```
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1               5                  10                  15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
            20                  25                  30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
        35                  40                  45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
    50                  55                  60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65                  70                  75                  80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
                85                  90                  95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
            100                 105                 110

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
        115                 120                 125

Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    130                 135                 140

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
145                 150                 155                 160

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
                165                 170                 175

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser
            180                 185                 190
```

```
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        195                 200                 205

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
    210                 215                 220

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
225                 230                 235                 240

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
                245                 250                 255

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            260                 265                 270

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        275                 280                 285

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
    290                 295                 300

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
305                 310                 315                 320

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                325                 330                 335

Leu Ser Leu Gly Lys Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly
            340                 345                 350

Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe Phe Lys Arg Gly Arg Lys
        355                 360                 365

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
    370                 375                 380

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
385                 390                 395                 400

Gly Gly Cys Glu Leu Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala
                405                 410                 415

Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
            420                 425                 430

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
        435                 440                 445
```

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
450 455 460

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
465 470 475 480

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
485 490 495

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
500 505 510

His Met Gln Ala Leu Pro Pro Arg
515 520

<210> 11
<211> 405
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 11
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1 5 10 15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
20 25 30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
35 40 45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
50 55 60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65 70 75 80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
85 90 95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
100 105 110

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
115 120 125

```
Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    130                 135                 140

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
145                 150                 155                 160

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
                165                 170                 175

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser
            180                 185                 190

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        195                 200                 205

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
    210                 215                 220

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
225                 230                 235                 240

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
                245                 250                 255

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            260                 265                 270

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        275                 280                 285

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
    290                 295                 300

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
305                 310                 315                 320

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                325                 330                 335

Leu Ser Leu Gly Lys Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly
            340                 345                 350

Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe Phe Lys Arg Gly Arg Lys
        355                 360                 365

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
    370                 375                 380
```

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
385 390 395 400

Gly Gly Cys Glu Leu
405

<210> 12
<211> 7754
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 12
gttagaccag atctgagcct gggagctctc tggctaacta gggaacccac tgcttaagcc 60

tcaataaagc ttgccttgag tgcttcaagt agtgtgtgcc cgtctgttgt gtgactctgg 120

taactagaga tccctcagac ccttttagtc agtgtggaaa atctctagca gtggcgcccg 180

aacagggact tgaaagcgaa agggaaacca gaggagctct ctcgacgcag gactcggctt 240

gctgaagcgc gcacggcaag aggcgagggg cggcgactgg tgagtacgcc aaaaattttg 300

actagcggag gctagaagga gagagatggg tgcgagagcg tcagtattaa gcgggggaga 360

attagatcga tgggaaaaaa ttcggttaag gccaggggga aagaaaaaat ataaattaaa 420

acatatagta tgggcaagca gggagctaga acgattcgca gttaatcctg gcctgttaga 480

aacatcagaa ggctgtagac aaatactggg acagctacaa ccatcccttc agacaggatc 540

agaagaactt agatcattat ataatacagt agcaaccctc tattgtgtgc atcaaaggat 600

agagataaaa gacaccaagg aagctttaga caagatagag gaagagcaaa acaaaagtaa 660

gaaaaaagca cagcaagcag cagctgacac aggacacagc aatcaggtca gccaaaatta 720

ccctatagtg cagaacatcc aggggcaaat ggtacatcag gccatatcac ctagaacttt 780

aaatgcatgg gtaaaagtag tagaagagaa ggctttcagc ccagaagtga tacccatgtt 840

ttcagcatta tcagaaggag ccaccccaca agatttaaac accatgctaa acacagtggg 900

gggacatcaa gcagccatgc aaatgttaaa agagaccatc aatgaggaag ctgcaggcaa 960

agagaagagt ggtgcagaga gaaaaaagag cagtgggaat aggagctttg ttccttgggt 1020

tcttgggagc agcaggaagc actatgggcg cagcgtcaat gacgctgacg gtacaggcca 1080

gacaattatt gtctggtata gtgcagcagc agaacaattt gctgagggct attgaggcgc 1140

aacagcatct gttgcaactc acagtctggg gcatcaagca gctccaggca agaatcctgg 1200

ctgtggaaag atacctaaag gatcaacagc tcctggggat ttggggttgc tctggaaaac 1260

tcatttgcac cactgctgtg ccttggatct acaaatggca gtattcatcc acaattttaa 1320

aagaaaaggg gggattgggg ggtacagtgc aggggaaaga atagtagaca taatagcaac 1380

agacatacaa actaaagaat tacaaaaaca aattacaaaa attcaaaatt ttcgggttta 1440

ttacagggac agcagagatc cagtttgggg atcaattgca tgaagaatct gcttagggtt 1500

aggcgttttg cgctgcttcg cgaggatctg cgatcgctcc ggtgcccgtc agtgggcaga 1560

gcgcacatcg cccacagtcc ccgagaagtt gggggggaggg gtcggcaatt gaaccggtgc 1620

ctagagaagg tggcgcgggg taaactggga aagtgatgtc gtgtactggc tccgcctttt 1680

tcccgagggt gggggagaac cgtatataag tgcagtagtc gccgtgaacg ttctttttcg 1740

caacgggttt gccgccagaa cacagctgaa gcttcgaggg gctcgcatct ctccttcacg 1800

cgcccgccgc cctacctgag gccgccatcc acgccggttg agtcgcgttc tgccgcctcc 1860

cgcctgtggt gcctcctgaa ctgcgtccgc cgtctaggta agtttaaagc tcaggtcgag 1920

accgggcctt tgtccggcgc tcccttggag cctacctaga ctcagccggc tctccacgct 1980

ttgcctgacc ctgcttgctc aactctacgt ctttgtttcg ttttctgttc tgcgccgtta 2040

cagatccaag ctgtgaccgg cgcctacggc tagcgccgcc accatgctgc tgctggtgac 2100

cagcctgctg ctgtgcgagc tgccccaccc cgcctttctg ctgatccctg gccccgtgcc 2160

ccctagcacc gccctgcgct acctgatcga ggaactggtg aacatcaccc agaaccagaa 2220

agccccccctg tgcaacggca gcatggtgtg gagcatcaac ctgaccgccg gcatgtactg 2280

tgccgccctg gaaagcctga tcaacgtgag cggctgcagc gccatcgaga aaacccagcg 2340

gatgctgtcc ggcttctgcc cccacaaggt gtccgccgga cagttcagca gcctgcacgt 2400

gcgggacacc aagatcgagg tggcccagtt cgtgaaggac ctgctgctgc acctgaagaa 2460

gctgttccgg gagggccggt tcaactacaa gaccaccccc cctgtgctgg acagcgacgg 2520

cagcttcttc ctgtacagca ggctgaccgt ggacaagagc cggtggcagg aaggcaacgt 2580

ctttagctgc agcgtgatgc acgaggccct gcacaaccac tacacccaga agagcctgtc 2640

cctgagcctg ggcaagcggg tgaagttcag ccggtccgcc gacgcccctg cctaccagca 2700

gggccagaac cagctgtaca acgagctgaa cctgggcagg cgggaggaat acgacgtgct 2760

ggacaagcgg agaggccggg accctgagat gggcggcaag cctcggcgga agaaccccca 2820

ggaaggcctg tataacgaac tgcagaaaga caagatggcc gaggcctaca gcgagatcgg 2880

catgaagggc gagcggaggc ggggcaaggg ccacgacggc ctgtatcagg gcctgtccac 2940

cgccaccaag gatacctacg acgccctgca catgcaggcc ctgccccccaa ggtctagacc 3000

cgggctgcag gaattcgata tcaagcttat cgataatcaa cctctggatt acaaaatttg 3060

tgaaagattg actggtattc ttaactatgt tgctcctttt acgctatgtg gatacgctgc 3120

tttaatgcct ttgtatcatg ctattgcttc ccgtatggct ttcattttct cctccttgta 3180

taaatcctgg ttgctgtctc tttatgagga gttgtggccc gttgtcaggc aacgtggcgt 3240

ggtgtgcact gtgtttgctg acgcaacccc cactggttgg ggcattgcca ccacctgtca 3300

gctcctttcc gggactttcg ctttcccccc ccctattgcc acggcggaac tcatcgccgc 3360

ctgccttgcc cgctgctgga caggggctcg gctgttgggc actgacaatt ccgtggtgtt 3420

gtcggggaaa tcatcgtcct ttccttggct gctcgcctgt gttgccacct ggattctgcg 3480

cgggacgtcc ttctgctacg tcccttcggc cctcaatcca gcggaccttc cttcccgcgg 3540

cctgctgccg gctctgcggc ctcttccgcg tcttcgcctt cgccctcaga cgagtcggat 3600

ctccctttgg gccgcctccc cgcatcgata ccgtcgacta gccgtacctt taagaccaat 3660

gacttacaag gcagctgtag atcttagcca ctttttaaaa gaaaaggggg gactggaagg 3720

gctaattcac tcccaaagaa gacaagatct gcttttgcc tgtactgggt ctctctggtt 3780

agaccagatc tgagcctggg agctctctgg ctaactaggg aacccactgc ttaagcctca 3840

ataaagcttg ccttgagtgc ttcaagtagt gtgtgcccgt ctgttgtgtg actctggtaa 3900

ctagagatcc ctcagaccct tttagtcagt gtggaaaatc tctagcagaa ttcgatatca 3960

agcttatcga taccgtcgac ctcgaggggg ggcccggtac ccaattcgcc ctatagtgag 4020

tcgtattaca attcactggc cgtcgtttta caacgtcgtg actgggaaaa ccctggcgtt 4080

acccaactta atcgccttgc agcacatccc cctttcgcca gctggcgtaa tagcgaagag 4140

gcccgcaccg atcgcccttc ccaacagttg cgcagcctga atggcgaatg gaaattgtaa 4200

gcgttaatat tttgttaaaa ttcgcgttaa atttttgtta aatcagctca ttttttaacc 4260

aataggccga atcggcaaa atcccttata aatcaaaaga atagaccgag atagggttga 4320

gtgttgttcc agtttggaac aagagtccac tattaaagaa cgtggactcc aacgtcaaag 4380

ggcgaaaaac cgtctatcag ggcgatggcc cactacgtga accatcaccc taatcaagtt 4440

ttttggggtc gaggtgccgt aaagcactaa atcggaaccc taaagggagc ccccgattta 4500

gagcttgacg gggaaagccg gcgaacgtgg cgagaaagga agggaagaaa gcgaaaggag 4560

cgggcgctag ggcgctggca agtgtagcgg tcacgctgcg cgtaaccacc acacccgccg 4620

cgcttaatgc gccgctacag ggcgcgtcag gtggcacttt tcggggaaat gtgcgcggaa 4680

cccctatttg tttatttttc taaatacatt caaatatgta tccgctcatg agacaataac 4740

cctgataaat gcttcaataa tattgaaaaa ggaagagtat gagtattcaa catttccgtg 4800

tcgcccttat tccctttttt gcggcatttt gccttcctgt ttttgctcac ccagaaacgc 4860

tggtgaaagt aaaagatgct gaagatcagt tgggtgcacg agtgggttac atcgaactgg 4920

atctcaacag cggtaagatc cttgagagtt ttcgccccga agaacgtttt ccaatgatga 4980

gcacttttaa agttctgcta tgtggcgcgg tattatcccg tattgacgcc gggcaagagc 5040

aactcggtcg ccgcatacac tattctcaga atgacttggt tgagtactca ccagtcacag 5100

aaaagcatct tacggatggc atgacagtaa gagaattatg cagtgctgcc ataaccatga 5160

gtgataacac tgcggccaac ttacttctga caacgatcgg aggaccgaag gagctaaccg 5220

ctttttgca caacatgggg gatcatgtaa ctcgccttga tcgttgggaa ccggagctga 5280

atgaagccat accaaacgac gagcgtgaca ccacgatgcc tgtagcaatg gcaacaacgt 5340

tgcgcaaact attaactggc gaactactta ctctagcttc ccggcaacaa ttaatagact 5400

ggatggaggc ggataaagtt gcaggaccac ttctgcgctc ggcccttccg gctggctggt 5460

ttattgctga taaatctgga gccggtgagc gtgggtctcg cggtatcatt gcagcactgg 5520

ggccagatgg taagccctcc cgtatcgtag ttatctacac gacggggagt caggcaacta 5580

tggatgaacg aaatagacag atcgctgaga taggtgcctc actgattaag cattggtaac 5640

tgtcagacca agtttactca tatatacttt agattgattt aaaacttcat ttttaattta 5700

aaaggatcta ggtgaagatc ctttttgata atctcatgac caaaatccct taacgtgagt 5760

tttcgttcca ctgagcgtca gaccccgtag aaaagatcaa aggatcttct tgagatcctt 5820

tttttctgcg cgtaatctgc tgcttgcaaa caaaaaaacc accgctacca gcggtggttt 5880

gtttgccgga tcaagagcta ccaactcttt ttccgaaggt aactggcttc agcagagcgc 5940

agataccaaa tactgttctt ctagtgtagc cgtagttagg ccaccacttc aagaactctg 6000

tagcaccgcc tacatacctc gctctgctaa tcctgttacc agtggctgct gccagtggcg 6060

ataagtcgtg tcttaccggg ttggactcaa gacgatagtt accggataag gcgcagcggt 6120

cgggctgaac gggggggttcg tgcacacagc ccagcttgga gcgaacgacc tacaccgaac 6180

tgagatacct acagcgtgag ctatgagaaa gcgccacgct tcccgaaggg agaaaggcgg 6240

acaggtatcc ggtaagcggc agggtcggaa caggagagcg cacgagggag cttccagggg 6300

gaaacgcctg gtatctttat agtcctgtcg ggtttcgcca cctctgactt gagcgtcgat 6360

ttttgtgatg ctcgtcaggg gggcggagcc tatggaaaaa cgccagcaac gcggcctttt 6420

tacggttcct ggccttttgc tggccttttg ctcacatgtt ctttcctgcg ttatcccctg 6480

attctgtgga taaccgtatt accgccttttg agtgagctga taccgctcgc cgcagccgaa 6540

cgaccgagcg cagcgagtca gtgagcgagg aagcggaaga gcgcccaata cgcaaaccgc 6600

ctctccccgc gcgttggccg attcattaat gcagctggca cgacaggttt cccgactgga 6660

aagcgggcag tgagcgcaac gcaattaatg tgagttagct cactcattag gcaccccagg 6720

ctttacactt tatgcttccg gctcgtatgt tgtgtggaat tgtgagcgga taacaatttc 6780

acacaggaaa cagctatgac catgattacg ccaagctcga aattaaccct cactaaaggg 6840

aacaaaagct ggagctccac cgcggtggcg gcctcgaggt cgagatccgg tcgaccagca 6900

accatagtcc cgcccctaac tccgcccatc ccgcccctaa ctccgcccag ttccgcccat 6960

tctccgcccc atggctgact aatttttttt atttatgcag aggccgaggc cgcctcggcc 7020

tctgagctat tccagaagta gtgaggaggc ttttttggag gcctaggctt ttgcaaaaag 7080

cttcgacggt atcgattggc tcatgtccaa cattaccgcc atgttgacat tgattattga 7140

ctagttatta atagtaatca attacggggt cattagttca tagcccatat atggagttcc 7200

gcgttacata acttacggta aatggcccgc ctggctgacc gcccaacgac ccccgcccat 7260

tgacgtcaat aatgacgtat gttcccatag taacgccaat agggactttc cattgacgtc 7320

aatgggtgga gtatttacgg taaactgccc acttggcagt acatcaagtg tatcatatgc 7380

caagtacgcc ccctattgac gtcaatgacg gtaaatggcc cgcctggcat tatgcccagt 7440

acatgacctt atgggacttt cctacttggc agtacatcta cgtattagtc atcgctatta 7500

ccatggtgat gcggttttgg cagtacatca atgggcgtgg atagcggttt gactcacggg 7560

gatttccaag tctccacccc attgacgtca atgggagttt gttttggcac caaaatcaac 7620

gggactttcc aaaatgtcgt aacaactccg ccccattgac gcaaatgggc ggtaggcgtg 7680

tacggaattc ggagtggcga gccctcagat cctgcatata agcagctgct ttttgcctgt 7740

actgggtctc tctg 7754

<210> 13
<211> 8732
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 13
gttagaccag atctgagcct gggagctctc tggctaacta gggaacccac tgcttaagcc 60

tcaataaagc ttgccttgag tgcttcaagt agtgtgtgcc cgtctgttgt gtgactctgg 120

taactagaga tccctcagac cctttttagtc agtgtggaaa atctctagca gtggcgcccg 180

aacagggact tgaaagcgaa agggaaacca gaggagctct ctcgacgcag gactcggctt 240

gctgaagcgc gcacggcaag aggcgagggg cggcgactgg tgagtacgcc aaaaattttg 300

actagcggag gctagaagga gagagatggg tgcgagagcg tcagtattaa gcgggggaga 360

attagatcga tgggaaaaaa ttcggttaag gccaggggga aagaaaaaat ataaattaaa 420

acatatagta tgggcaagca gggagctaga acgattcgca gttaatcctg gcctgttaga 480

aacatcagaa ggctgtagac aaatactggg acagctacaa ccatcccttc agacaggatc 540

agaagaactt agatcattat ataatacagt agcaaccctc tattgtgtgc atcaaaggat 600

agagataaaa gacaccaagg aagctttaga caagatagag gaagagcaaa acaaaagtaa 660

gaaaaaagca cagcaagcag cagctgacac aggacacagc aatcaggtca gccaaaatta 720

ccctatagtg cagaacatcc aggggcaaat ggtacatcag gccatatcac ctagaacttt 780

aaatgcatgg gtaaaagtag tagaagagaa ggctttcagc ccagaagtga tacccatgtt 840

ttcagcatta tcagaaggag ccaccccaca agatttaaac accatgctaa acacagtggg 900

gggacatcaa gcagccatgc aaatgttaaa agagaccatc aatgaggaag ctgcaggcaa 960

agagaagagt ggtgcagaga gaaaaaagag cagtgggaat aggagctttg ttccttgggt 1020

tcttgggagc agcaggaagc actatgggcg cagcgtcaat gacgctgacg gtacaggcca 1080

gacaattatt gtctggtata gtgcagcagc agaacaattt gctgagggct attgaggcgc 1140

aacagcatct gttgcaactc acagtctggg gcatcaagca gctccaggca agaatcctgg 1200

ctgtggaaag atacctaaag gatcaacagc tcctggggat ttggggttgc tctggaaaac 1260

tcatttgcac cactgctgtg ccttggatct acaaatggca gtattcatcc acaattttaa 1320

aagaaaaggg gggattgggg ggtacagtgc aggggaaaga atagtagaca taatagcaac 1380

agacatacaa actaaagaat tacaaaaaca aattacaaaa attcaaaatt ttcgggttta 1440

ttacagggac agcagagatc cagtttgggg atcaattgca tgaagaatct gcttagggtt 1500

aggcgttttg cgctgcttcg cgaggatctg cgatcgctcc ggtgcccgtc agtgggcaga 1560

gcgcacatcg cccacagtcc ccgagaagtt ggggggaggg gtcggcaatt gaaccggtgc 1620

ctagagaagg tggcgcgggg taaactggga aagtgatgtc gtgtactggc tccgcctttt 1680

tcccgagggt gggggagaac cgtatataag tgcagtagtc gccgtgaacg ttctttttcg 1740

caacgggttt gccgccagaa cacagctgaa gcttcgaggg gctcgcatct ctccttcacg 1800

cgcccgccgc cctacctgag gccgccatcc acgccggttg agtcgcgttc tgccgcctcc 1860

cgcctgtggt gcctcctgaa ctgcgtccgc cgtctaggta agtttaaagc tcaggtcgag 1920

accgggcctt tgtccggcgc tcccttggag cctacctaga ctcagccggc tctccacgct 1980

ttgcctgacc ctgcttgctc aactctacgt ctttgtttcg ttttctgttc tgcgccgtta 2040

cagatccaag ctgtgaccgg cgcctacggc tagcgccgcc accatgctgc tgctggtgac 2100

cagcctgctg ctgtgcgagc tgccccaccc cgcctttctg ctgatccccg acatccagat 2160

gacccagacc acctccagcc tgagcgccag cctgggcgac cgggtgacca tcagctgccg 2220

ggccagccag gacatcagca agtacctgaa ctggtatcag cagaagcccg acggcaccgt 2280

caagctgctg atctaccaca ccagccggct gcacagcggc gtgcccagcc ggtttagcgg 2340

cagcggctcc ggcaccgact acagcctgac catctccaac ctggaacagg aagatatcgc 2400

cacctacttt tgccagcagg gcaacacact gccctacacc tttggcggcg gaacaaagct 2460

ggaaatcacc ggcagcacct ccggcagcgg caagcctggc agcggcgagg gcagcaccaa 2520

gggcgaggtg aagctgcagg aaagcggccc tggcctggtg gcccccagcc agagcctgag 2580

cgtgacctgc accgtgagcg gcgtgagcct gcccgactac ggcgtgagct ggatccggca 2640

gccccccagg aagggcctgg aatggctggg cgtgatctgg ggcagcgaga ccacctacta 2700

caacagcgcc ctgaagagcc ggctgaccat catcaaggac aacagcaaga gccaggtgtt 2760

cctgaagatg aacagcctgc agaccgacga caccgccatc tactactgcg ccaagcacta 2820

ctactacggc ggcagctacg ccatggacta ctggggccag ggcaccagcg tgaccgtgag 2880

cagcgagagc aagtacggcc ctccctgccc cccttgccct gcccccgagt tcctgggcgg 2940

acccagcgtg ttcctgttcc cccccaagcc caaggacacc ctgatgatca gccggacccc 3000

cgaggtgacc tgcgtggtgg tggacgtgag ccaggaagat cccgaggtcc agttcaattg 3060

gtacgtggac ggcgtggagg tgcacaacgc caagaccaag cccagggaag agcagttcaa 3120

cagcacctac cgggtggtgt ccgtgctgac cgtgctgcac caggactggc tgaacggcaa 3180

agaatacaag tgcaaggtgt ccaacaaggg cctgcccagc agcatcgaga aaaccatcag 3240

caaggccaag ggccagcctc gggagcccca ggtgtacacc ctgccccctt cccaggaaga 3300

gatgaccaag aatcaggtgt ccctgacctg cctggtgaag ggcttctacc ccagcgacat 3360

cgccgtggag tgggagagca acggccagcc cgagaacaac tacaagacca ccccccctgt 3420

gctggacagc gacggcagct tcttcctgta cagcaggctg accgtggaca agagccggtg 3480

gcaggaaggc aacgtcttta gctgcagcgt gatgcacgag gccctgcaca accactacac 3540

ccagaagagc ctgtccctga gcctgggcaa gatggccctg atcgtgctgg gcggcgtggc 3600

cgggctgctg ctgttcatcg gcctgggcat ctttttccgg gtgaagttca gccggtccgc 3660

cgacgccccc gcctaccagc agggccagaa ccagctgtac aacgagctga acctgggcag 3720

gcgggaggaa tacgacgtgc tggacaagcg gagaggccgg gaccctgaga tgggcggcaa 3780

gcccaggcgg aagaaccctc aggaaggcct gtataacgaa ctgcagaaag acaagatggc 3840

cgaggcctac agcgagatcg gcatgaaggg cgagcggcgg aggggcaagg gccacgacgg 3900

cctgtaccag ggcctgagca ccgccaccaa ggatacctac gacgccctgc acatgcaggc 3960

cctgcccccc aggtgacccg ggctgcagga attcgatatc aagcttatcg ataatcaacc 4020

tctggattac aaaatttgtg aaagattgac tggtattctt aactatgttg ctccttttac 4080

gctatgtgga tacgctgctt taatgccttt gtatcatgct attgcttccc gtatggcttt 4140

cattttctcc tccttgtata aatcctggtt gctgtctctt tatgaggagt tgtggcccgt 4200

tgtcaggcaa cgtggcgtgg tgtgcactgt gtttgctgac gcaaccccca ctggttgggg 4260

cattgccacc acctgtcagc tcctttccgg gactttcgct ttccccctcc ctattgccac 4320

ggcggaactc atcgccgcct gccttgcccg ctgctggaca ggggctcggc tgttgggcac 4380

tgacaattcc gtggtgttgt cggggaaatc atcgtccttt ccttggctgc tcgcctgtgt 4440

tgccacctgg attctgcgcg ggacgtcctt ctgctacgtc ccttcggccc tcaatccagc 4500

ggaccttcct tcccgcggcc tgctgccggc tctgcggcct cttccgcgtc ttcgccttcg 4560

ccctcagacg agtcggatct ccctttgggc cgcctccccg catcgatacc gtcgactagc 4620

cgtaccttta agaccaatga cttacaaggc agctgtagat cttagccact ttttaaaaga 4680

aaaggggga ctggaagggc taattcactc ccaaagaaga caagatctgc tttttgcctg 4740

tactgggtct ctctggttag accagatctg agcctgggag ctctctggct aactagggaa 4800

cccactgctt aagcctcaat aaagcttgcc ttgagtgctt caagtagtgt gtgcccgtct 4860

gttgtgtgac tctggtaact agagatccct cagacccttt tagtcagtgt ggaaaatctc 4920

tagcagaatt cgatatcaag cttatcgata ccgtcgacct cgaggggggg cccggtaccc 4980

aattcgccct atagtgagtc gtattacaat tcactggccg tcgttttaca acgtcgtgac 5040

tgggaaaacc ctggcgttac ccaacttaat cgccttgcag cacatccccc tttcgccagc 5100

tggcgtaata gcgaagaggc ccgcaccgat cgcccttccc aacagttgcg cagcctgaat 5160

ggcgaatgga aattgtaagc gttaatattt tgttaaaatt cgcgttaaat ttttgttaaa 5220

tcagctcatt ttttaaccaa taggccgaaa tcggcaaaat cccttataaa tcaaaagaat 5280

agaccgagat agggttgagt gttgttccag tttggaacaa gagtccacta ttaaagaacg 5340

tggactccaa cgtcaaaggg cgaaaaaccg tctatcaggg cgatggccca ctacgtgaac 5400

catcacccta atcaagtttt ttggggtcga ggtgccgtaa agcactaaat cggaacccta 5460

aagggagccc ccgatttaga gcttgacggg gaaagccggc gaacgtggcg agaaaggaag 5520

ggaagaaagc gaaaggagcg ggcgctaggg cgctggcaag tgtagcggtc acgctgcgcg 5580

taaccaccac acccgccgcg cttaatgcgc cgctacaggg cgcgtcaggt ggcacttttc 5640

ggggaaatgt gcgcggaacc cctatttgtt tatttttcta aatacattca aatatgtatc 5700

cgctcatgag acaataaccc tgataaatgc ttcaataata ttgaaaaagg aagagtatga 5760

gtattcaaca tttccgtgtc gcccttattc cctttttgc ggcattttgc cttcctgttt 5820

ttgctcaccc agaaacgctg gtgaaagtaa aagatgctga agatcagttg ggtgcacgag 5880

tgggttacat cgaactggat ctcaacagcg gtaagatcct tgagagtttt cgccccgaag 5940

aacgttttcc aatgatgagc acttttaaag ttctgctatg tggcgcggta ttatcccgta 6000

ttgacgccgg gcaagagcaa ctcggtcgcc gcatacacta ttctcagaat gacttggttg 6060

agtactcacc agtcacagaa aagcatctta cggatggcat gacagtaaga gaattatgca 6120

gtgctgccat aaccatgagt gataacactg cggccaactt acttctgaca acgatcggag 6180

gaccgaagga gctaaccgct tttttgcaca acatggggga tcatgtaact cgccttgatc 6240

gttgggaacc ggagctgaat gaagccatac caaacgacga gcgtgacacc acgatgcctg 6300

tagcaatggc aacaacgttg cgcaaactat taactggcga actacttact ctagcttccc 6360

ggcaacaatt aatagactgg atggaggcgg ataaagttgc aggaccactt ctgcgctcgg 6420

cccttccggc tggctggttt attgctgata aatctggagc cggtgagcgt gggtctcgcg 6480

gtatcattgc agcactgggg ccagatggta agccctcccg tatcgtagtt atctacacga 6540

cggggagtca ggcaactatg gatgaacgaa atagacagat cgctgagata ggtgcctcac 6600

tgattaagca ttggtaactg tcagaccaag tttactcata tatactttag attgatttaa 6660

aacttcattt ttaatttaaa aggatctagg tgaagatcct ttttgataat ctcatgacca 6720

aaatccctta acgtgagttt tcgttccact gagcgtcaga ccccgtagaa aagatcaaag 6780

gatcttcttg agatcctttt tttctgcgcg taatctgctg cttgcaaaca aaaaaaccac 6840

cgctaccagc ggtggtttgt ttgccggatc aagagctacc aactcttttt ccgaaggtaa 6900

ctggcttcag cagagcgcag ataccaaata ctgttcttct agtgtagccg tagttaggcc 6960

accacttcaa gaactctgta gcaccgccta catacctcgc tctgctaatc ctgttaccag 7020

tggctgctgc cagtggcgat aagtcgtgtc ttaccgggtt ggactcaaga cgatagttac 7080

cggataaggc gcagcggtcg ggctgaacgg ggggttcgtg cacacagccc agcttggagc 7140

gaacgaccta caccgaactg agatacctac agcgtgagct atgagaaagc gccacgcttc 7200

ccgaagggag aaaggcggac aggtatccgg taagcggcag ggtcggaaca ggagagcgca 7260

cgagggagct tccagggggа aacgcctggt atctttatag tcctgtcggg tttcgccacc 7320

tctgacttga gcgtcgattt ttgtgatgct cgtcaggggg gcggagccta tggaaaaacg 7380

ccagcaacgc ggcctttta cggttcctgg ccttttgctg gccttttgct cacatgttct 7440

ttcctgcgtt atcccctgat tctgtggata accgtattac cgcctttgag tgagctgata 7500

ccgctcgccg cagccgaacg accgagcgca gcgagtcagt gagcgaggaa gcggaagagc 7560

gcccaatacg caaaccgcct ctccccgcgc gttggccgat tcattaatgc agctggcacg 7620

acaggtttcc cgactggaaa gcgggcagtg agcgcaacgc aattaatgtg agttagctca 7680

ctcattaggc accccaggct ttacacttta tgcttccggc tcgtatgttg tgtggaattg 7740

tgagcggata acaatttcac acaggaaaca gctatgacca tgattacgcc aagctcgaaa 7800

ttaaccctca ctaaagggaa caaaagctgg agctccaccg cggtggcggc ctcgaggtcg 7860

agatccggtc gaccagcaac catagtcccg cccctaactc cgcccatccc gcccctaact 7920

ccgcccagtt ccgcccattc tccgccccat ggctgactaa ttttttttat ttatgcagag 7980

gccgaggccg cctcggcctc tgagctattc cagaagtagt gaggaggctt ttttggaggc 8040

ctaggctttt gcaaaaagct tcgacggtat cgattggctc atgtccaaca ttaccgccat 8100

gttgacattg attattgact agttattaat agtaatcaat tacggggtca ttagttcata 8160

gcccatatat ggagttccgc gttacataac ttacggtaaa tggcccgcct ggctgaccgc 8220

ccaacgaccc ccgcccattg acgtcaataa tgacgtatgt tcccatagta acgccaatag 8280

ggactttcca ttgacgtcaa tgggtggagt atttacggta aactgcccac ttggcagtac 8340

atcaagtgta tcatatgcca agtacgcccc ctattgacgt caatgacggt aaatggcccg 8400

cctggcatta tgcccagtac atgaccttat gggactttcc tacttggcag tacatctacg 8460

tattagtcat cgctattacc atggtgatgc ggttttggca gtacatcaat gggcgtggat 8520

agcggtttga ctcacgggga tttccaagtc tccaccccat tgacgtcaat gggagtttgt 8580

tttggcacca aaatcaacgg gactttccaa aatgtcgtaa caactccgcc ccattgacgc 8640

aaatgggcgg taggcgtgta cggaattcgg agtggcgagc cctcagatcc tgcatataag 8700

cagctgcttt ttgcctgtac tgggtctctc tg 8732

<210> 14
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 14
Gly Gly Gly Ser Ser Gly Gly Gly Ser Gly
1 5 10

<210> 15
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 15
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1 5 10

<210> 16
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 16
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gly Gly Ser
1 5 10 15

Ser Gly Gly Gly Ser Gly
20

<210> 17
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 17
Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn
1 5 10 15

Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu
20 25 30

Phe Pro Gly Pro Ser Lys Pro
35

<210> 18
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 18
Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
1 5 10 15

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
20 25 30

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
35 40 45

<210> 19
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 19
Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala

1 5 10 15

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
20 25 30

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
35 40 45

<210> 20
<211> 129
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 20
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gly Gly Ser
1 5 10 15

Ser Gly Gly Gly Ser Gly Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
20 25 30

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
35 40 45

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
50 55 60

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
65 70 75 80

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
85 90 95

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
100 105 110

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
115 120 125

Lys

<210> 21
<211> 21
<212> PRT
<213> Homo sapiens

<400> 21
Leu Cys Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly Val Ile Leu
1 5 10 15

Thr Ala Leu Phe Leu
20

<210> 22
<211> 27
<212> PRT
<213> Homo sapiens

<400> 22
Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1 5 10 15

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val
20 25

<210> 23
<211> 21
<212> PRT
<213> Homo sapiens

<400> 23
Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr
20

<210> 24
<211> 23
<212> PRT
<213> Homo sapiens

<400> 24
Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr Leu Tyr
20

<210> 25
<211> 24
<212> PRT
<213> Homo sapiens

<400> 25
Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr Leu Tyr Cys
20

<210> 26
<211> 27
<212> PRT
<213> Homo sapiens

<400> 26
Ile Ile Ser Phe Phe Leu Ala Leu Thr Ser Thr Ala Leu Leu Phe Leu
1 5 10 15

Leu Phe Phe Leu Thr Leu Arg Phe Ser Val Val
20 25

<210> 27
<211> 41
<212> PRT
<213> Homo sapiens

<400> 27
Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
1 5 10 15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
20 25 30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser
35 40

<210> 28
<211> 41
<212> PRT
<213> Homo sapiens

<400> 28
Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr
1 5 10 15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
20 25 30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser
35 40

<210> 29
<211> 42
<212> PRT
<213> Homo sapiens

<400> 29
Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1 5 10 15

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe

20 25 30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
35 40

<210> 30
<211> 42
<212> PRT
<213> Homo sapiens

<400> 30
Ala Leu Tyr Leu Leu Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His
1 5 10 15

Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln
20 25 30

Ala Asp Ala His Ser Thr Leu Ala Lys Ile
35 40

<210> 31
<211> 362
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 31
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Gly Pro Val Pro Pro Ser Thr Ala Leu Arg
20 25 30

Tyr Leu Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro
35 40 45

Leu Cys Asn Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met
50 55 60

Tyr Cys Ala Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala
65 70 75 80

Ile Glu Lys Thr Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val
85 90 95

Ser Ala Gly Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu
100 105 110

```
Val Ala Gln Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe
        115                 120                 125

Arg Glu Gly Arg Phe Asn Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
    130                 135                 140

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
145                 150                 155                 160

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
                165                 170                 175

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
            180                 185                 190

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Lys Arg Gly
        195                 200                 205

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
    210                 215                 220

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
225                 230                 235                 240

Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val Lys Phe Ser Arg
                245                 250                 255

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
            260                 265                 270

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
        275                 280                 285

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
    290                 295                 300

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
305                 310                 315                 320

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
                325                 330                 335

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
            340                 345                 350

Ala Leu His Met Gln Ala Leu Pro Pro Arg
        355                 360
```

<210> 32
<211> 410
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 32

```
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                  10                  15

Ala Phe Leu Leu Ile Pro Gly Pro Val Pro Pro Ser Thr Ala Leu Arg
            20                  25                  30

Tyr Leu Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro
        35                  40                  45

Leu Cys Asn Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met
    50                  55                  60

Tyr Cys Ala Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala
65                  70                  75                  80

Ile Glu Lys Thr Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val
                85                  90                  95

Ser Ala Gly Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu
            100                 105                 110

Val Ala Gln Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe
        115                 120                 125

Arg Glu Gly Arg Phe Asn Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
    130                 135                 140

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
145                 150                 155                 160

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
                165                 170                 175

Leu Asp Phe Ala Cys Asp Phe Trp Val Leu Val Val Val Gly Gly Val
            180                 185                 190

Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp
        195                 200                 205
```

```
Val Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met
    210                 215                 220

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
225                 230                 235                 240

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Gly Gly Gly Lys Arg Gly
                245                 250                 255

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
            260                 265                 270

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
        275                 280                 285

Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val Lys Phe Ser Arg
    290                 295                 300

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
305                 310                 315                 320

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                325                 330                 335

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            340                 345                 350

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        355                 360                 365

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    370                 375                 380

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
385                 390                 395                 400

Ala Leu His Met Gln Ala Leu Pro Pro Arg
                405                 410
```

<210> 33
<211> 442
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 33

```
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                  10                  15

Ala Phe Leu Leu Ile Pro Gly Pro Val Pro Pro Ser Thr Ala Leu Arg
            20                  25                  30

Tyr Leu Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro
        35                  40                  45

Leu Cys Asn Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met
    50                  55                  60

Tyr Cys Ala Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala
65                  70                  75                  80

Ile Glu Lys Thr Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val
                85                  90                  95

Ser Ala Gly Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu
            100                 105                 110

Val Ala Gln Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe
        115                 120                 125

Arg Glu Gly Arg Phe Asn Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
    130                 135                 140

Cys Pro Gly Gly Gly Ser Ser Gly Gly Gly Ser Gly Gly Gln Pro Arg
145                 150                 155                 160

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
                165                 170                 175

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
            180                 185                 190

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
        195                 200                 205

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
    210                 215                 220

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
225                 230                 235                 240

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
```

245 250 255

Leu Ser Leu Ser Leu Gly Lys Met Ala Leu Ile Val Leu Gly Gly Val
260 265 270

Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe Phe Lys Arg Gly
275 280 285

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
290 295 300

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
305 310 315 320

Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val Lys Phe Ser Arg
325 330 335

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
340 345 350

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
355 360 365

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
370 375 380

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
385 390 395 400

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
405 410 415

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
420 425 430

Ala Leu His Met Gln Ala Leu Pro Pro Arg
435 440

<210> 34
<211> 541
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 34
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro

```
1               5                   10                  15

Ala Phe Leu Leu Ile Pro Gly Pro Val Pro Pro Ser Thr Ala Leu Arg
            20                  25                  30

Tyr Leu Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro
        35                  40                  45

Leu Cys Asn Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met
    50                  55                  60

Tyr Cys Ala Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala
65                  70                  75                  80

Ile Glu Lys Thr Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val
                85                  90                  95

Ser Ala Gly Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu
            100                 105                 110

Val Ala Gln Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe
        115                 120                 125

Arg Glu Gly Arg Phe Asn Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
    130                 135                 140

Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro
145                 150                 155                 160

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
                165                 170                 175

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
            180                 185                 190

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
        195                 200                 205

Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
    210                 215                 220

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
225                 230                 235                 240

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
                245                 250                 255
```

```
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
            260                 265                 270

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
        275                 280                 285

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
    290                 295                 300

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
305                 310                 315                 320

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
                325                 330                 335

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
            340                 345                 350

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Ile Tyr Ile Trp Ala
        355                 360                 365

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
    370                 375                 380

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
385                 390                 395                 400

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
                405                 410                 415

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val Lys
            420                 425                 430

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
        435                 440                 445

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
    450                 455                 460

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
465                 470                 475                 480

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
                485                 490                 495

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
            500                 505                 510
```

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
515 520 525

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
530 535 540

<210> 35
<211> 373
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 35
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Gly Pro Val Pro Pro Ser Thr Ala Leu Arg
20 25 30

Tyr Leu Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro
35 40 45

Leu Cys Asn Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met
50 55 60

Tyr Cys Ala Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala
65 70 75 80

Ile Glu Lys Thr Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val
85 90 95

Ser Ala Gly Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu
100 105 110

Val Ala Gln Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe
115 120 125

Arg Glu Gly Arg Phe Asn Gly Gly Gly Ser Ser Gly Gly Gly Ser Gly
130 135 140

Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
145 150 155 160

Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg
165 170 175

```
Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
            180                 185                 190

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
        195                 200                 205

Ala Ala Tyr Arg Ser Gly Gly Gly Lys Arg Gly Arg Lys Lys Leu Leu
    210                 215                 220

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
225                 230                 235                 240

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
                245                 250                 255

Glu Leu Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
            260                 265                 270

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
        275                 280                 285

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
    290                 295                 300

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
305                 310                 315                 320

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
                325                 330                 335

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
            340                 345                 350

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
        355                 360                 365

Ala Leu Pro Pro Arg
    370
```

<210> 36
<211> 385
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 36

```
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                  10                  15

Ala Phe Leu Leu Ile Pro Gly Pro Val Pro Pro Ser Thr Ala Leu Arg
            20                  25                  30

Tyr Leu Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro
        35                  40                  45

Leu Cys Asn Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met
    50                  55                  60

Tyr Cys Ala Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala
65                  70                  75                  80

Ile Glu Lys Thr Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val
                85                  90                  95

Ser Ala Gly Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu
            100                 105                 110

Val Ala Gln Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe
        115                 120                 125

Arg Glu Gly Arg Phe Asn Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
    130                 135                 140

Cys Pro Gly Gly Gly Ser Ser Gly Gly Gly Ser Gly Met Phe Trp Val
145                 150                 155                 160

Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr
                165                 170                 175

Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Gly Gly
            180                 185                 190

His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg
        195                 200                 205

Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg
    210                 215                 220

Ser Gly Gly Gly Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
225                 230                 235                 240

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
                245                 250                 255
```

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Gly Gly
260 265 270

Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
275 280 285

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
290 295 300

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
305 310 315 320

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
325 330 335

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
340 345 350

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
355 360 365

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
370 375 380

Arg
385

<210> 37
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 37
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Gly Pro Val Pro Pro Ser Thr Ala Leu Arg
20 25 30

Tyr Leu Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro
35 40 45

Leu Cys Asn Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met
50 55 60

```
Tyr Cys Ala Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala
65                  70                  75                  80

Ile Glu Lys Thr Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val
                85                  90                  95

Ser Ala Gly Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu
            100                 105                 110

Val Ala Gln Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe
        115                 120                 125

Arg Glu Gly Arg Phe Asn Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
    130                 135                 140

Cys Pro Gly Gly Gly Ser Ser Gly Gly Gly Ser Gly Gly Gln Pro Arg
145                 150                 155                 160

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
                165                 170                 175

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
            180                 185                 190

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
        195                 200                 205

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
    210                 215                 220

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
225                 230                 235                 240

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
                245                 250                 255

Leu Ser Leu Ser Leu Gly Lys Met Phe Trp Val Leu Val Val Val Gly
            260                 265                 270

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
        275                 280                 285

Phe Trp Val Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met
    290                 295                 300

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
```

305 310 315 320

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Gly Gly Gly Lys
325 330 335

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
340 345 350

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
355 360 365

Glu Glu Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val Lys Phe
370 375 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
385 390 395 400

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
405 410 415

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
420 425 430

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
435 440 445

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
450 455 460

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465 470 475 480

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 38
<211> 592
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 38
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Gly Pro Val Pro Pro Ser Thr Ala Leu Arg

```
                20                  25                  30

Tyr Leu Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro
        35                  40                  45

Leu Cys Asn Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met
    50                  55                  60

Tyr Cys Ala Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala
65                  70                  75                  80

Ile Glu Lys Thr Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val
                85                  90                  95

Ser Ala Gly Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu
            100                 105                 110

Val Ala Gln Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe
        115                 120                 125

Arg Glu Gly Arg Phe Asn Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
    130                 135                 140

Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro
145                 150                 155                 160

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
                165                 170                 175

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
            180                 185                 190

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
        195                 200                 205

Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
    210                 215                 220

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
225                 230                 235                 240

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
                245                 250                 255

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
            260                 265                 270
```

```
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
        275                 280                 285

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
    290                 295                 300

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
305                 310                 315                 320

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
                325                 330                 335

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
            340                 345                 350

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Phe Trp Val Leu
        355                 360                 365

Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val
    370                 375                 380

Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Gly Gly His
385                 390                 395                 400

Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys
                405                 410                 415

His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
            420                 425                 430

Gly Gly Gly Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
        435                 440                 445

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
    450                 455                 460

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly
465                 470                 475                 480

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
                485                 490                 495

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
            500                 505                 510

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
        515                 520                 525
```

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
530 535 540

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
545 550 555 560

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
565 570 575

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
580 585 590

<210> 39
<211> 340
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 39
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1 5 10 15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
20 25 30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
35 40 45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
50 55 60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65 70 75 80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
85 90 95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
100 105 110

Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
115 120 125

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
130 135 140

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
145 150 155 160

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
165 170 175

Ser Leu Val Ile Thr Leu Tyr Lys Arg Gly Arg Lys Lys Leu Leu Tyr
180 185 190

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
195 200 205

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
210 215 220

Leu Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
225 230 235 240

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
245 250 255

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
260 265 270

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
275 280 285

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
290 295 300

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
305 310 315 320

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
325 330 335

Leu Pro Pro Arg
340

<210> 40
<211> 388
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 40

```
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1               5                  10                  15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
            20                  25                  30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
        35                  40                  45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
    50                  55                  60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65                  70                  75                  80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
                85                  90                  95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
            100                 105                 110

Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
        115                 120                 125

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
    130                 135                 140

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
145                 150                 155                 160

Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
                165                 170                 175

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser
            180                 185                 190

Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly
        195                 200                 205

Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala
    210                 215                 220

Ala Tyr Arg Ser Gly Gly Gly Lys Arg Gly Arg Lys Lys Leu Leu Tyr
225                 230                 235                 240

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
                245                 250                 255
```

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
260 265 270

Leu Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
275 280 285

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
290 295 300

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
305 310 315 320

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
325 330 335

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
340 345 350

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
355 360 365

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
370 375 380

Leu Pro Pro Arg
385

<210> 41
<211> 420
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 41
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1 5 10 15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
20 25 30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
35 40 45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
50 55 60

```
Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65                  70                  75                  80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
                85                  90                  95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
            100                 105                 110

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gly Gly Ser
        115                 120                 125

Ser Gly Gly Gly Ser Gly Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    130                 135                 140

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
145                 150                 155                 160

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                165                 170                 175

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            180                 185                 190

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
        195                 200                 205

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    210                 215                 220

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
225                 230                 235                 240

Lys Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe
                245                 250                 255

Ile Gly Leu Gly Ile Phe Phe Lys Arg Gly Arg Lys Lys Leu Leu Tyr
            260                 265                 270

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
        275                 280                 285

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
    290                 295                 300

Leu Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
```

305 310 315 320

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
325 330 335

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
340 345 350

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
355 360 365

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
370 375 380

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
385 390 395 400

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
405 410 415

Leu Pro Pro Arg
420

<210> 42
<211> 519
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 42
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1 5 10 15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
20 25 30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
35 40 45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
50 55 60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65 70 75 80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys

85 90 95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
100 105 110

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
115 120 125

Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
130 135 140

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
145 150 155 160

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
165 170 175

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser
180 185 190

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
195 200 205

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
210 215 220

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
225 230 235 240

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
245 250 255

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
260 265 270

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
275 280 285

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
290 295 300

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
305 310 315 320

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
325 330 335

Leu Ser Leu Gly Lys Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
340 345 350

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Lys Arg Gly Arg Lys Lys
355 360 365

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
370 375 380

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
385 390 395 400

Gly Cys Glu Leu Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp
405 410 415

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
420 425 430

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
435 440 445

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
450 455 460

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
465 470 475 480

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
485 490 495

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
500 505 510

Met Gln Ala Leu Pro Pro Arg
515

<210> 43
<211> 351
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 43
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1 5 10 15

```
Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
            20                  25                  30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
        35                  40                  45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
    50                  55                  60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65                  70                  75                  80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
                85                  90                  95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
            100                 105                 110

Gly Gly Gly Ser Ser Gly Gly Gly Ser Gly Met Phe Trp Val Leu Val
        115                 120                 125

Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala
    130                 135                 140

Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Gly Gly His Ser
145                 150                 155                 160

Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His
                165                 170                 175

Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Gly
            180                 185                 190

Gly Gly Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
        195                 200                 205

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
    210                 215                 220

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg
225                 230                 235                 240

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
                245                 250                 255

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
            260                 265                 270
```

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
275 280 285

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
290 295 300

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
305 310 315 320

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
325 330 335

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
340 345 350

<210> 44
<211> 363
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 44
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1 5 10 15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
20 25 30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
35 40 45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
50 55 60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65 70 75 80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
85 90 95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
100 105 110

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gly Gly Ser
115 120 125

Ser Gly Gly Gly Ser Gly Met Phe Trp Val Leu Val Val Val Gly Gly
130 135 140

Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe
145 150 155 160

Trp Val Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn
165 170 175

Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
180 185 190

Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Gly Gly Gly Lys Arg
195 200 205

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
210 215 220

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
225 230 235 240

Glu Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val Lys Phe Ser
245 250 255

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
260 265 270

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
275 280 285

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
290 295 300

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
305 310 315 320

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
325 330 335

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
340 345 350

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
355 360

<210> 45
<211> 470

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 45

```
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1               5                  10                  15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
            20                  25                  30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
        35                  40                  45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
    50                  55                  60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65                  70                  75                  80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
                85                  90                  95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
            100                 105                 110

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gly Gly Ser
        115                 120                 125

Ser Gly Gly Gly Ser Gly Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    130                 135                 140

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
145                 150                 155                 160

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                165                 170                 175

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            180                 185                 190

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
        195                 200                 205

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    210                 215                 220
```

```
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
225                 230                 235                 240

Lys Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr
                245                 250                 255

Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys
            260                 265                 270

Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg
        275                 280                 285

Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp
    290                 295                 300

Phe Ala Ala Tyr Arg Ser Gly Gly Gly Lys Arg Gly Arg Lys Lys Leu
305                 310                 315                 320

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
                325                 330                 335

Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
            340                 345                 350

Cys Glu Leu Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
        355                 360                 365

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
    370                 375                 380

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
385                 390                 395                 400

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
                405                 410                 415

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
            420                 425                 430

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
        435                 440                 445

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
    450                 455                 460

Gln Ala Leu Pro Pro Arg
```

465 470

<210> 46
<211> 570
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 46

```
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1               5                  10                  15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
            20                  25                  30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
        35                  40                  45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
    50                  55                  60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65                  70                  75                  80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
                85                  90                  95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
            100                 105                 110

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
        115                 120                 125

Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    130                 135                 140

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
145                 150                 155                 160

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
                165                 170                 175

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser
            180                 185                 190

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
```

```
        195                 200                 205

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
    210                 215                 220

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
225                 230                 235                 240

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
                245                 250                 255

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            260                 265                 270

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        275                 280                 285

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
    290                 295                 300

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
305                 310                 315                 320

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                325                 330                 335

Leu Ser Leu Gly Lys Met Phe Trp Val Leu Val Val Val Gly Gly Val
            340                 345                 350

Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp
        355                 360                 365

Val Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met
    370                 375                 380

Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala
385                 390                 395                 400

Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Gly Gly Gly Lys Arg Gly
                405                 410                 415

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
            420                 425                 430

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
        435                 440                 445
```

Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val Lys Phe Ser Arg
450 455 460

Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
465 470 475 480

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
485 490 495

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
500 505 510

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
515 520 525

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
530 535 540

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
545 550 555 560

Ala Leu His Met Gln Ala Leu Pro Pro Arg
565 570

<210> 47
<211> 363
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 47
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Gly Pro Val Pro Pro Ser Thr Ala Leu Arg
20 25 30

Tyr Leu Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro
35 40 45

Leu Cys Asn Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met
50 55 60

Tyr Cys Ala Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala
65 70 75 80

```
Ile Glu Lys Thr Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val
                85                  90                  95

Ser Ala Gly Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu
            100                 105                 110

Val Ala Gln Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe
        115                 120                 125

Arg Glu Gly Arg Phe Asn Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
    130                 135                 140

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
145                 150                 155                 160

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
                165                 170                 175

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
            180                 185                 190

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Gly Gly Gly Lys Arg
        195                 200                 205

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
    210                 215                 220

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
225                 230                 235                 240

Glu Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val Lys Phe Ser
                245                 250                 255

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
            260                 265                 270

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
        275                 280                 285

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
    290                 295                 300

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
305                 310                 315                 320

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
                325                 330                 335
```

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
340 345 350

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
355 360

<210> 48
<211> 341
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 48
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1 5 10 15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
20 25 30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
35 40 45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
50 55 60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65 70 75 80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
85 90 95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
100 105 110

Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
115 120 125

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
130 135 140

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
145 150 155 160

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
165 170 175

```
Ser Leu Val Ile Thr Gly Gly Gly Lys Arg Gly Arg Lys Lys Leu Leu
            180                 185                 190

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
        195                 200                 205

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
    210                 215                 220

Glu Leu Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
225                 230                 235                 240

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
                245                 250                 255

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
            260                 265                 270

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
        275                 280                 285

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
    290                 295                 300

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
305                 310                 315                 320

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
                325                 330                 335

Ala Leu Pro Pro Arg
            340
```

<210> 49
<211> 112
<212> PRT
<213> Homo sapiens

<400> 49

```
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
1               5                   10                  15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
            20                  25                  30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
        35                  40                  45
```

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
100 105 110

<210> 50
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 50
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
1 5 10 15

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
100 105

<210> 51
<211> 229
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polypeptide"

<400> 51

```
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                  10                  15

Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Gln Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145                 150                 155                 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Lys
225
```

<210> 52
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 52
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro
1 5 10

<210> 53
<211> 229
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 53
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
1 5 10 15

Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Gln Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
100 105 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
115 120 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
130 135 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala

```
145                 150                 155                 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Lys
225
```

<210> 54
<211> 28
<212> PRT
<213> Homo sapiens

<400> 54

```
Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
1               5                   10                  15

Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val
            20                  25
```

Claims

1. A chimeric antigen receptor comprising

   (i) a binding domain comprising SEQ ID NO: 3 with, optionally, up to 5 single amino acid substitutions, provided that the amino acid at position 11 of SEQ ID NO: 3 is an amino acid other than E;
   (ii) a transmembrane domain selected from: a CD4 transmembrane domain or variant thereof having 1-5 amino acid substitutions, a CD8 transmembrane domain or variant thereof having 1-5 amino acid substitutions, a CD28 transmembrane domain or a variant thereof having 1-5 amino acid substitutions, and a CD3ζ transmembrane domain or a variant thereof having 1-5 amino acid substitutions;
   (iii) a costimulatory domain selected from the group consisting of: a CD28 costimulatory domain or a variant thereof having 1-5 amino acid substitutions, a 4IBB costimulatory domain or a variant thereof having 1-5 amino acid substitutions and an OX40 costimulatory domain or a variant thereof having 1-5 amino acid substitutions; and
   (iv) CD3ζ signaling domain or a variant thereof having 1-5 amino acid substitutions.

2. The chimeric antigen receptor of claim 1, wherein the binding domain comprises SEQ ID NO: 3, the transmembrane domain comprises a CD4 transmembrane domain, the costimulatory domain comprises a 41BB costimulatory domain, and the CD3ζ signaling domain is not a variant.

3. The chimeric antigen receptor of claim 1 or 2, wherein the chimeric antigen receptor comprises SEQ ID NO: 10.

4. The chimeric antigen receptor according to any one of claims 1-3 further comprising a GMSCFRa signal sequence.

5. The chimeric antigen receptor of claim 5, wherein the GMSCFRa signal sequence comprises SEQ ID NO: 2.

6. The chimeric antigen receptor according to any one of claims 1-5 further comprising a T2A ribosome skip.

7. The chimeric antigen receptor of claim 6, wherein T2A ribosome skip sequence comprises SEQ ID NO: 8.

8. The chimeric antigen receptor according to any one of claims 1-7 further comprising a truncated CD 19.

9. The chimeric antigen receptor of claim 8, wherein the truncated CD19 comprises SEQ IE NO: 9.

10. A population of human T cells that express the chimeric antigen receptor according to any one of claims 1-9.

11. The population of human T cells of claim 10, wherein the T cells comprise central memory T cells.

12. A composition for use in treating cancer in a patient, the composition comprising the population of human T cells according to claim 10 or 11.

13. The composition of claim 12, wherein the human T cells are autologous to the patient.

14. The composition of claim 12, wherein the human T cells are allogeneic to the patient.

15. The composition according to any one of claims 12-14, wherein the cancer is glioblastoma.

FIGURE 1

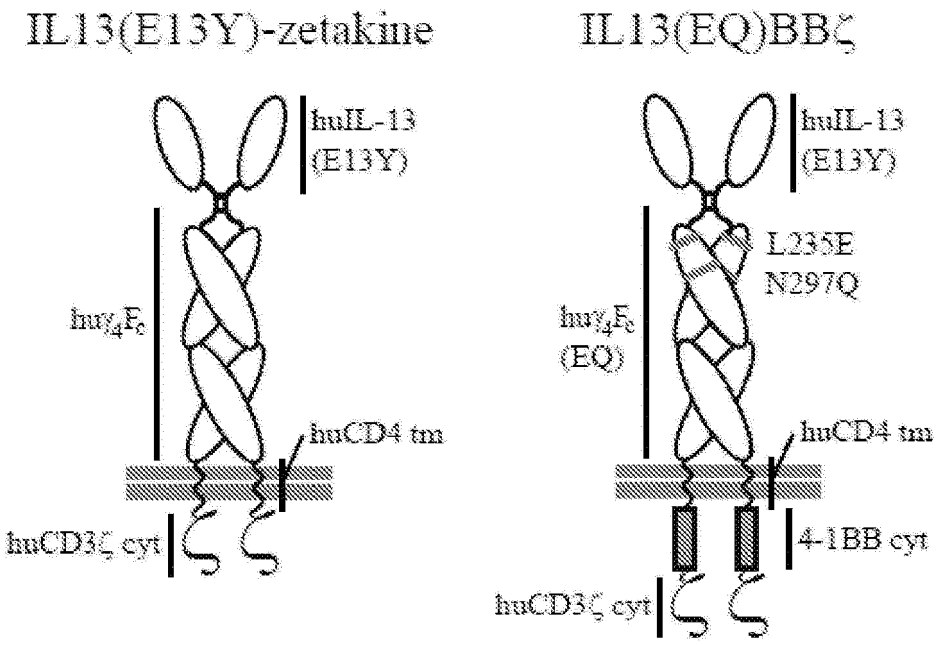

IL13(E13Y)-zetakine
huIL-13
(E13Y)
huγ4Fc
huCD4 tm
huCD3ζ cyt
IL13(EQ)BBζ
huIL-13
(E13Y)
L235E
N297Q
huγ4Fc
(EQ)
huCD4 tm
4-1BB cyt
huCD3ζ cyt

FIGURE 2

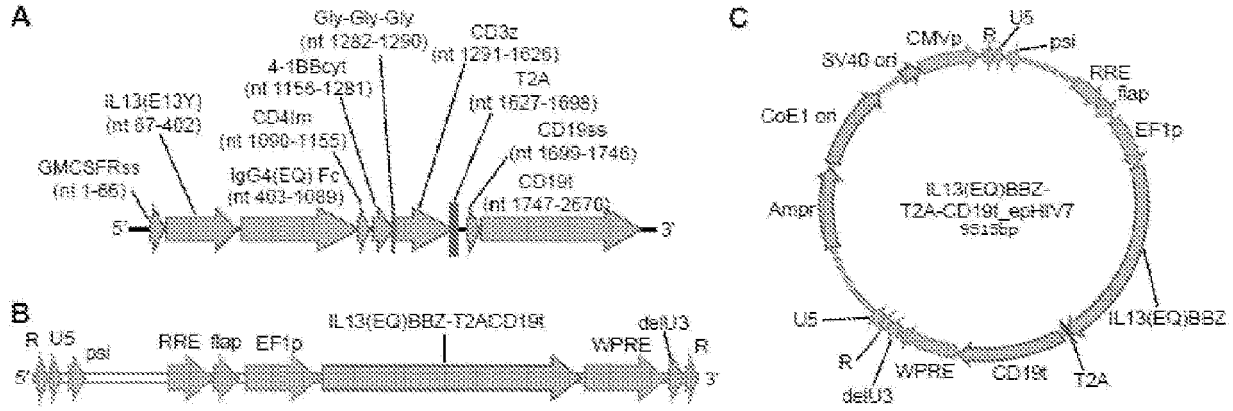

A
GMCSFRss
(nt 1-66)
IL13(E13Y)
(nt 67-402)
IgG4(EQ) Fc
(nt 403-1089)
CD4tm
(nt 1090-1155)
4-1BBcyt
(nt 1156-1281)
Gly-Gly-Gly
(nt 1282-1290)
CD3z
(nt 1291-1626)
T2A
(nt 1627-1698)
CD19ss
(nt 1699-1746)
CD19t
(nt 1747-2670)
5'
3'
B
R U5
psi
RRE
flap
EF1p
IL13(EQ)BBZ-T2ACD19t
WPRE
delU3
R
5'
3'
C
CMVp
R
U5
psi
SV40 ori
RRE
flap
CoE1 ori
EF1p
Ampr
IL13(EQ)BBZ-
T2A-CD19t_epHIV7
9513bp
U5
IL13(EQ)BBZ
R
WPRE
CD19t
T2A
delU3

FIGURE 3

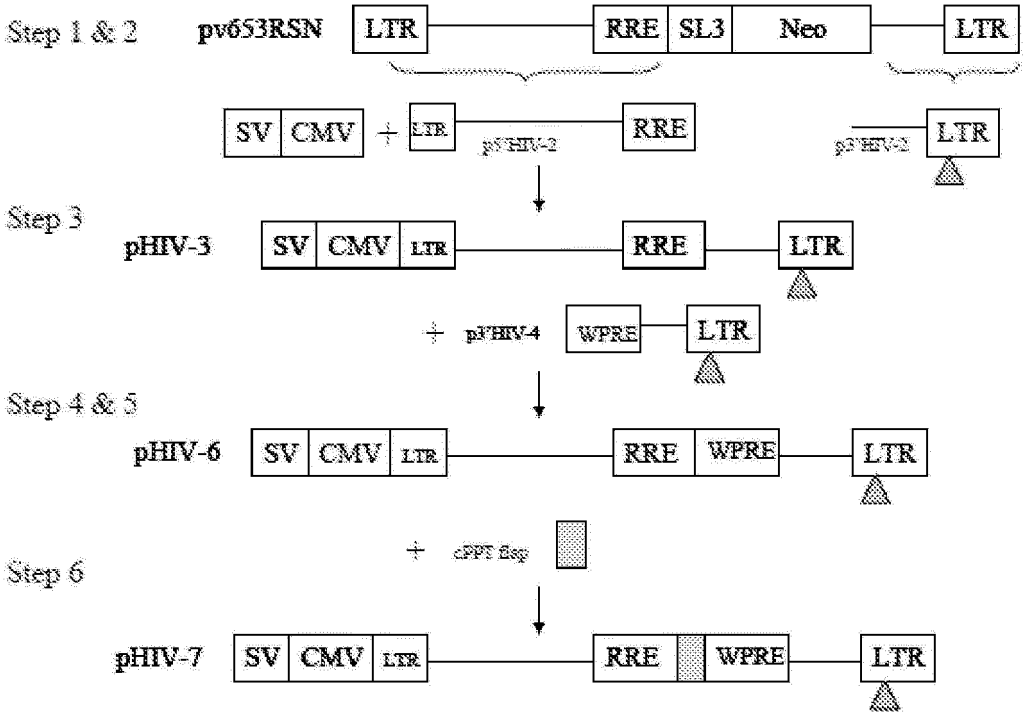

Step 1 & 2
pv653RSN
LTR
RRE
SL3
Neo
LTR
SV
CMV
LTR
RRE
LTR
Step 3
pHIV-3
SV
CMV
LTR
RRE
LTR
WPRE
LTR
Step 4 & 5
pHIV-6
SV
CMV
LTR
RRE
WPRE
LTR
Step 6
pHIV-7
SV
CMV
LTR
RRE
WPRE
LTR

FIGURE 4

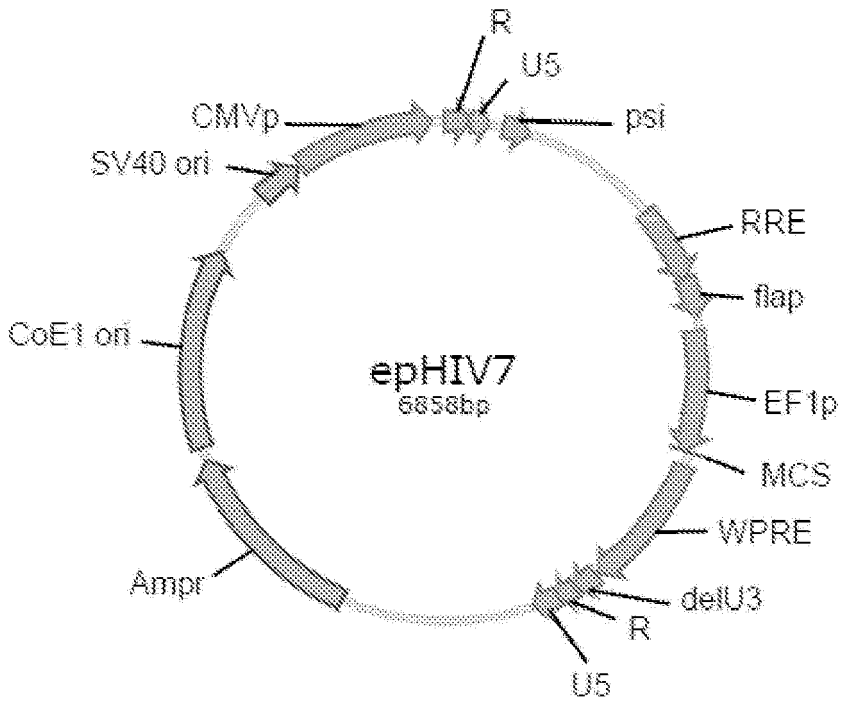

R
U5
psi
RRE
flap
EF1p
MCS
WPRE
delU3
R
U5
Ampr
CoE1 ori
SV40 ori
CMVp
epHIV7
6858bp

FIGURE 5

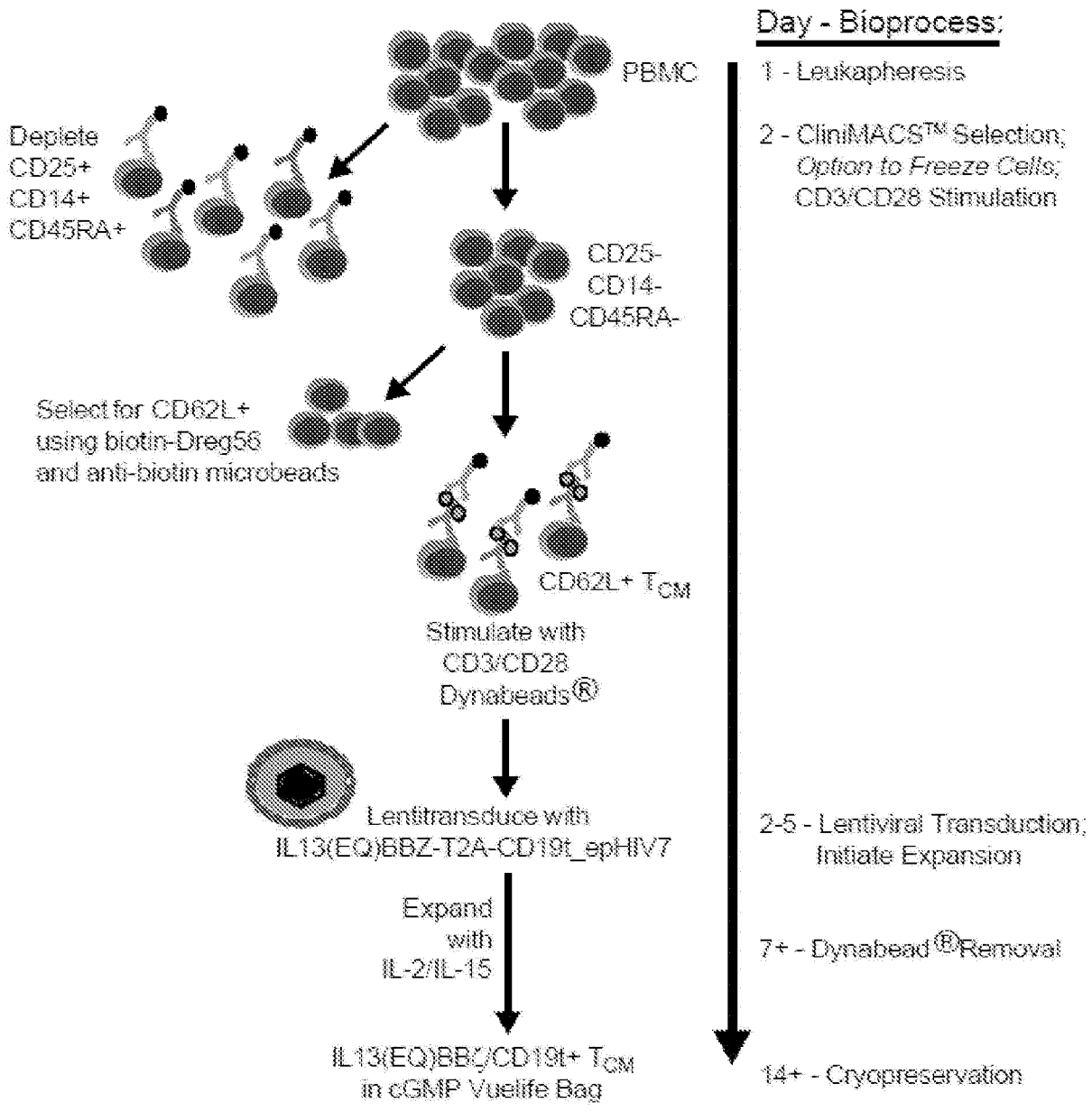

Day - Bioprocess:
PBMC
1 - Leukapheresis
Deplete
CD25+
CD14+
CD45RA+
2 - CliniMACS™ Selection;
Option to Freeze Cells;
CD3/CD28 Stimulation
CD25-
CD14-
CD45RA-
Select for CD62L+
using biotin-Dreg56
and anti-biotin microbeads
CD62L+ TCM
Stimulate with
CD3/CD28
Dynabeads®
Lentitransduce with
IL13(EQ)BBZ-T2A-CD19t_epHIV7
2-5 - Lentiviral Transduction;
Initiate Expansion
Expand
with
IL-2/IL-15
7+ - Dynabead® Removal
IL13(EQ)BBζ/CD19t+ TCM
in cGMP Vuelife Bag
14+ - Cryopreservation

FIGURE 6

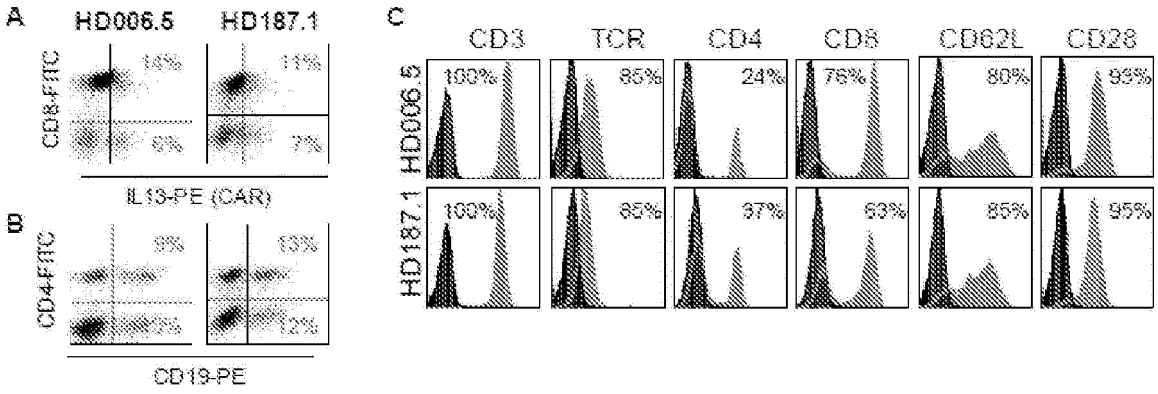
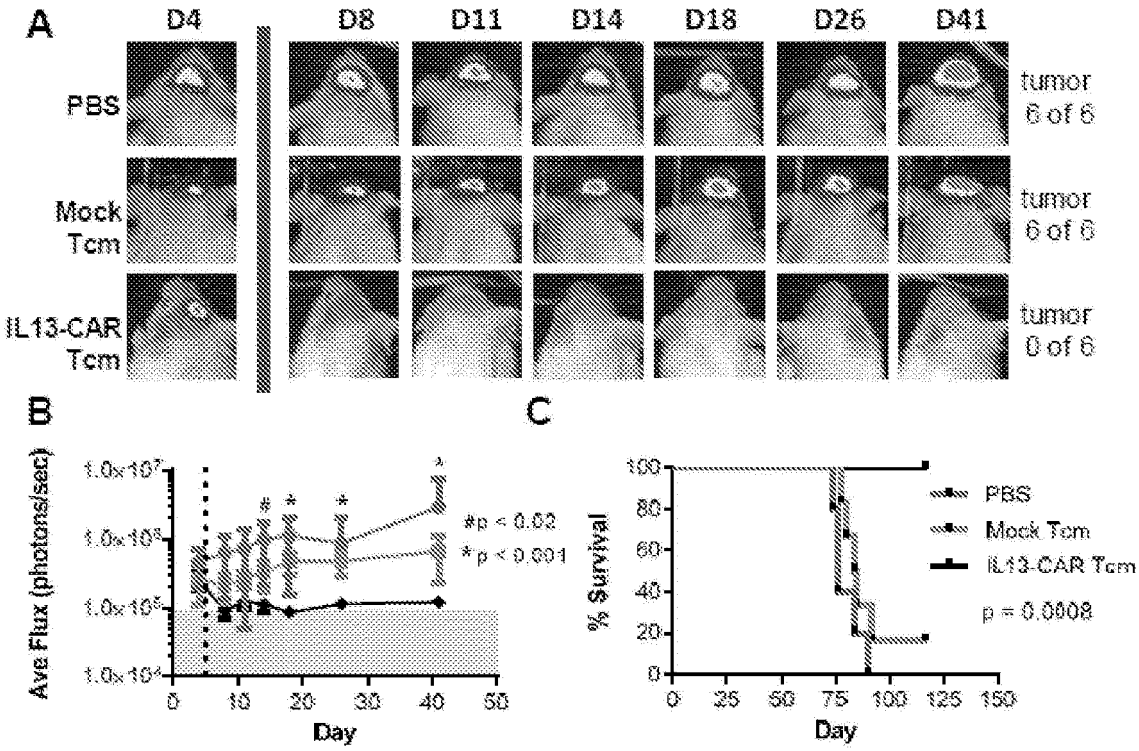

A
HD006.5
HD187.1
CD8-FITC
16%
11%
6%
7%
IL13-PE (CAR)
B
CD4-FITC
9%
13%
3%
12%
CD19-PE
C
CD3
TCR
CD4
CD8
CD62L
CD28
HD006.5
100%
85%
24%
76%
80%
93%
HD187.1
100%
85%
97%
63%
85%
95%

FIGURE 7


A
> 9x
> 3x
% Specific Lysis
40
30
20
10
0
HD006.5
HD187.1
K562
K562-IL13Rα2
PBT030-2
B
4000
3000
2000
1000
0
INF-γ (pg/ml)
HD006.5
HD187.1

FIGURE 8


A
D4
D8
D11
D14
D18
D26
D41
PBS
Mock Tcm
IL13-CAR Tcm
tumor 6 of 6
tumor 6 of 6
tumor 0 of 6
B
Ave Flux (photons/sec)
1.0x10^7
1.0x10^6
1.0x10^5
1.0x10^4
0
10
20
30
40
50
Day
#p < 0.02
*p < 0.001
C
% Survival
100
80
60
40
20
0
0
25
50
75
100
125
150
Day
PBS
Mock Tcm
IL13-CAR Tcm
p = 0.0008

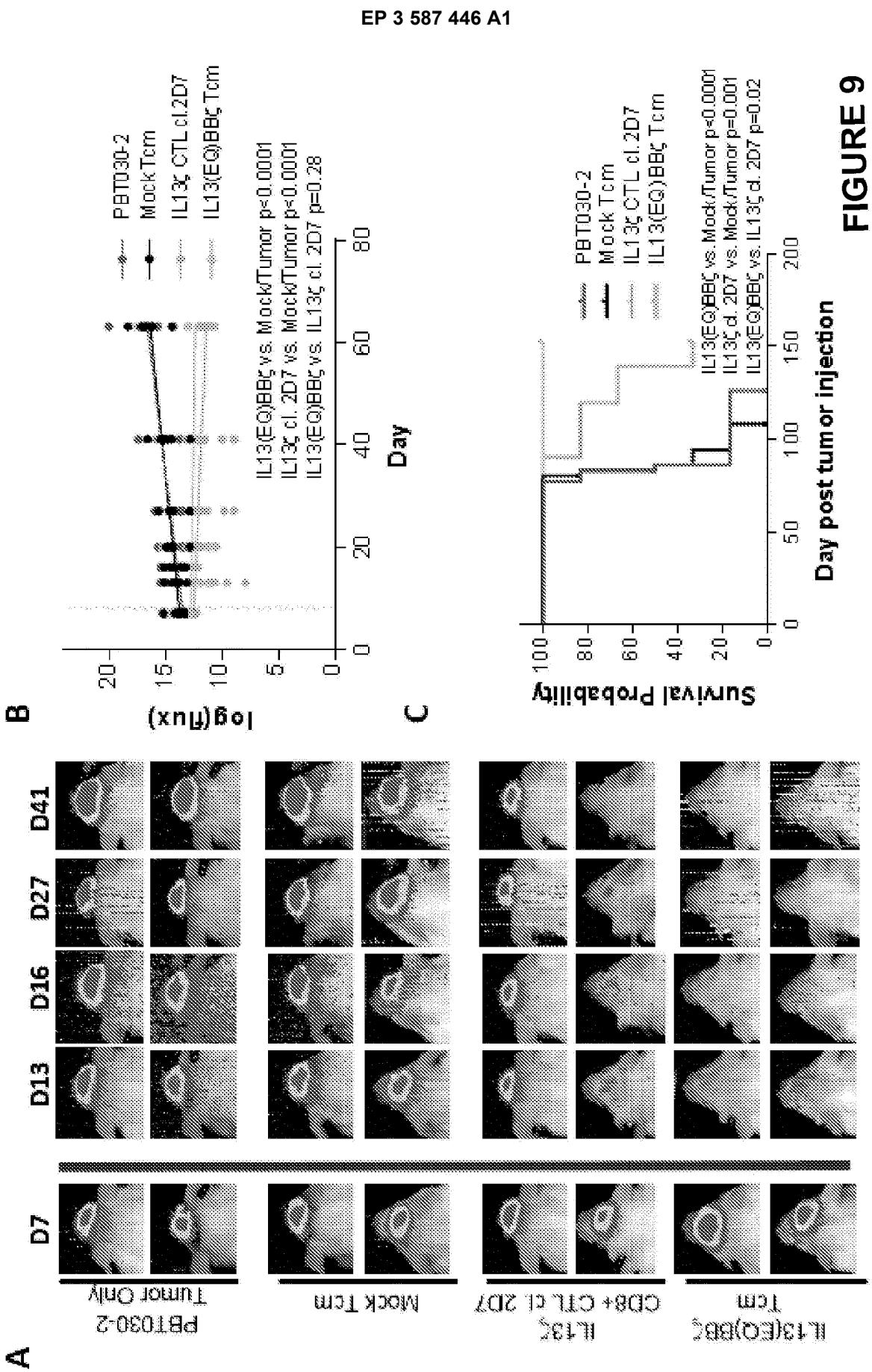

A
D7
D13
D16
D27
D41
PBT030-2 Tumor Only
Mock Tcm
IL13ζ CD8+ CTL cl. 2D7
IL13(EQ)BBζ Tcm
B
log(flux)
Day
PBT030-2
Mock Tcm
IL13ζ CTL cl.2D7
IL13(EQ)BBζ Tcm
IL13(EQ)BBζ vs. Mock/Tumor p<0.0001
IL13ζ cl. 2D7 vs. Mock/Tumor p<0.0001
IL13(EQ)BBζ vs. IL13ζ cl. 2D7 p=0.28
C
Survival Probability
Day post tumor injection
PBT030-2
Mock Tcm
IL13ζ CTL cl.2D7
IL13(EQ)BBζ Tcm
IL13(EQ)BBζ vs. Mock/Tumor p<0.0001
IL13ζ cl. 2D7 vs. Mock/Tumor p=0.001
IL13(EQ)BBζ vs. IL13ζ cl. 2D7 p=0.02

FIGURE 9

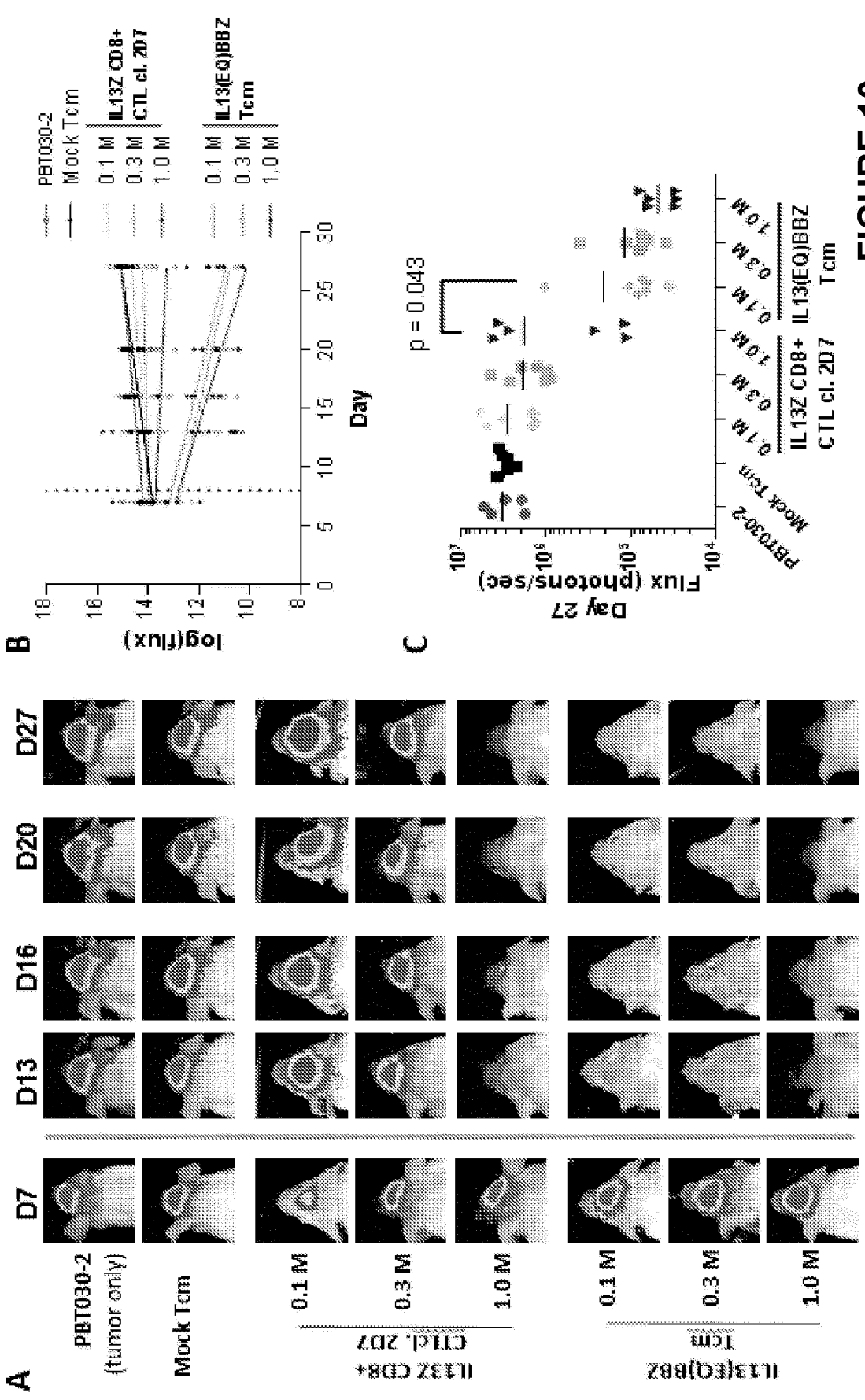

A
D7
D13
D16
D20
D27
PBT030-2 (tumor only)
Mock Tcm
IL13Z CD8+ CTL cl. 2D7
0.1 M
0.3 M
1.0 M
IL13(EQ)BBZ Tcm
B
PBT030-2
Mock Tcm
IL13Z CD8+ CTL cl. 2D7
IL13(EQ)BBZ Tcm
log(flux)
Day
C
p = 0.043
Day 27
Flux (photons/sec)
PBT030-2
Mock Tcm
IL13Z CD8+ CTL cl. 2D7
IL13(EQ)BBZ Tcm

FIGURE 10

FIGURE 11

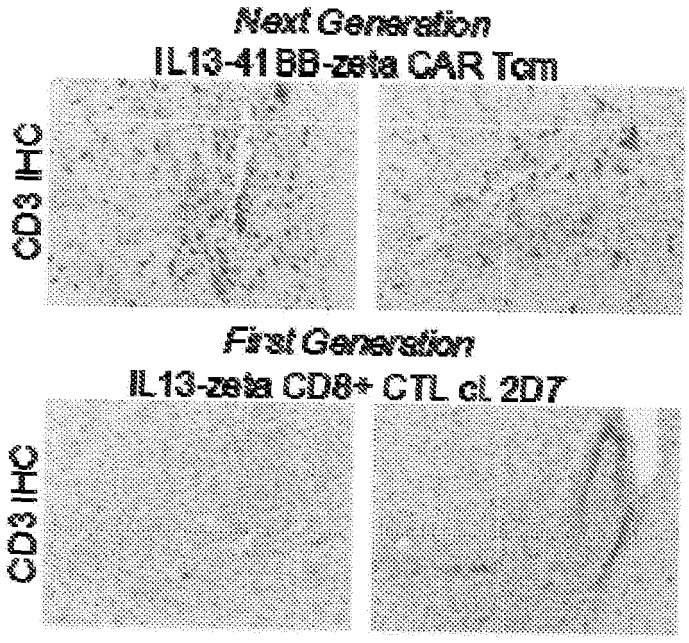
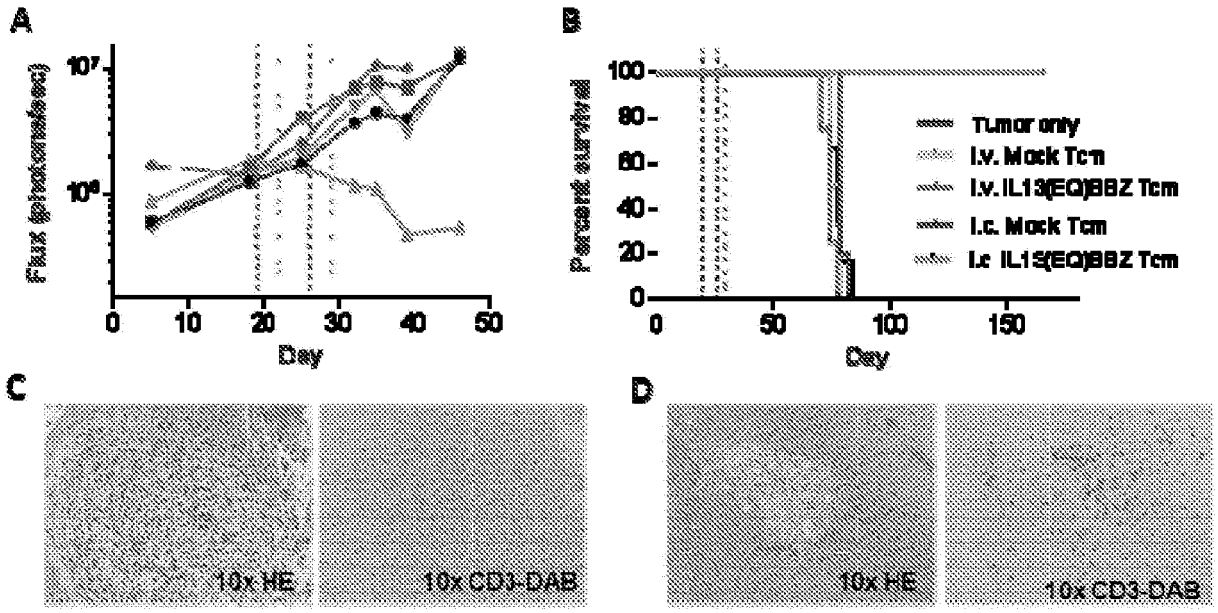

Next Generation
IL13-41BB-zeta CAR Tcm
CD3 IHC
First Generation
IL13-zeta CD8+ CTL cL 2D7
CD3 IHC

FIGURE 12


A
Flux (photons/sec)
Day
B
Percent survival
Tumor only
I.v. Mock Tcm
I.v. IL13(EQ)BBZ Tcm
I.c. Mock Tcm
I.c IL13(EQ)BBZ Tcm
Day
C
10x HE
10x CD3-DAB
D
10x HE
10x CD3-DAB

A
PBT030-2
left & right
hemisphere
IL13BBz CAR
T cells
i.c.t. vs. i.c.v.
B
Left Tumor -CD3
Right Tumor -CD3
i.c.t.
i.c.v.

FIGURE 13

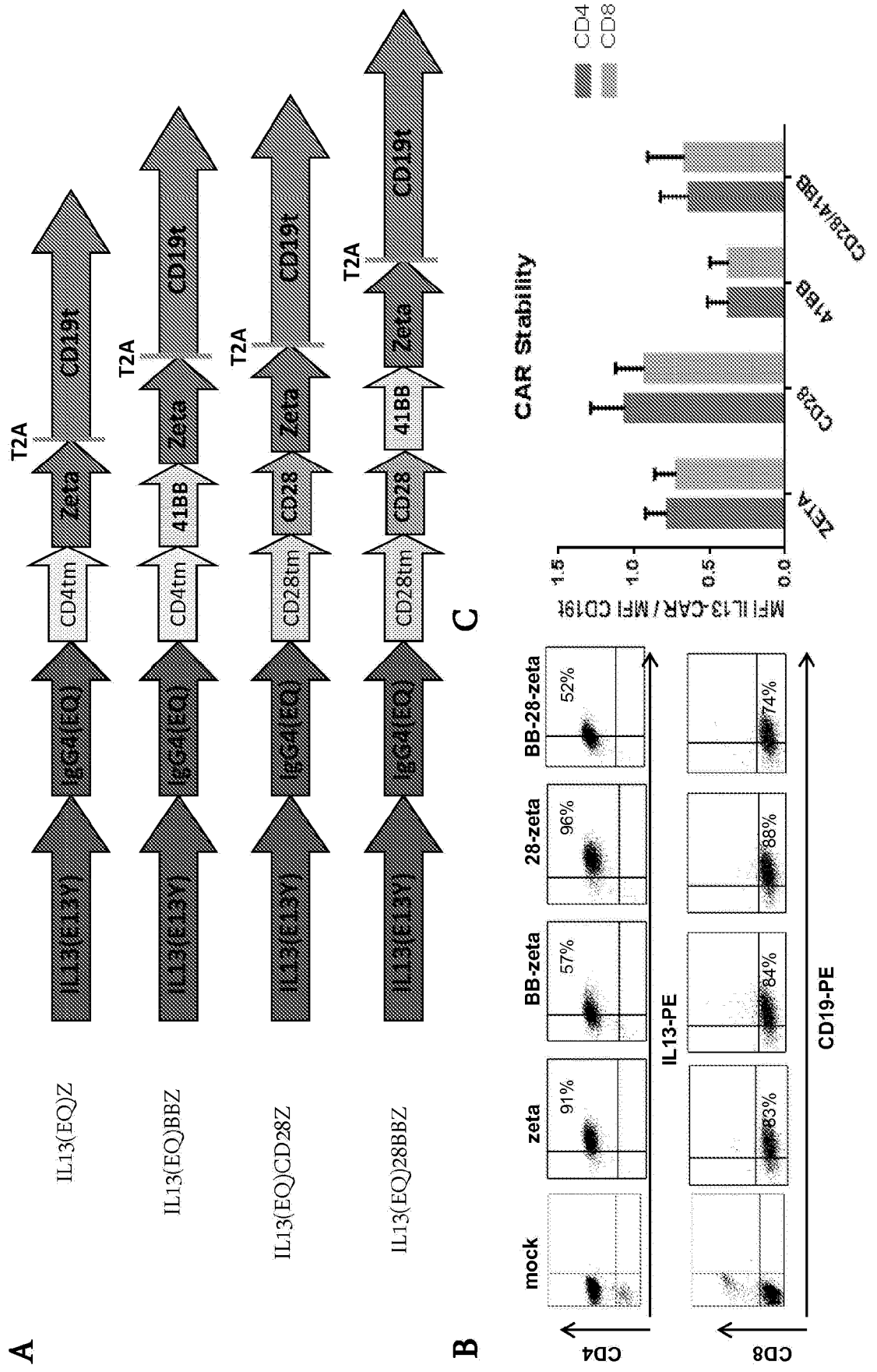

A
IL13(EQ)Z
IL13(EQ)BBZ
IL13(EQ)CD28Z
IL13(EQ)28BBZ
IL13(E13Y)
IgG4(EQ)
CD4tm
CD28tm
Zeta
41BB
CD28
T2A
CD19t
B
mock
zeta
BB-zeta
28-zeta
BB-28-zeta
91%
57%
96%
52%
84%
88%
74%
83%
CD4
CD8
IL13-PE
CD19-PE
C
CAR Stability
CD4
CD8
MFI IL13-CAR / MFI CD19t
1.5
1.0
0.5
0.0
ZETA
CD28
41BB
CD28/41BB

FIGURE 14

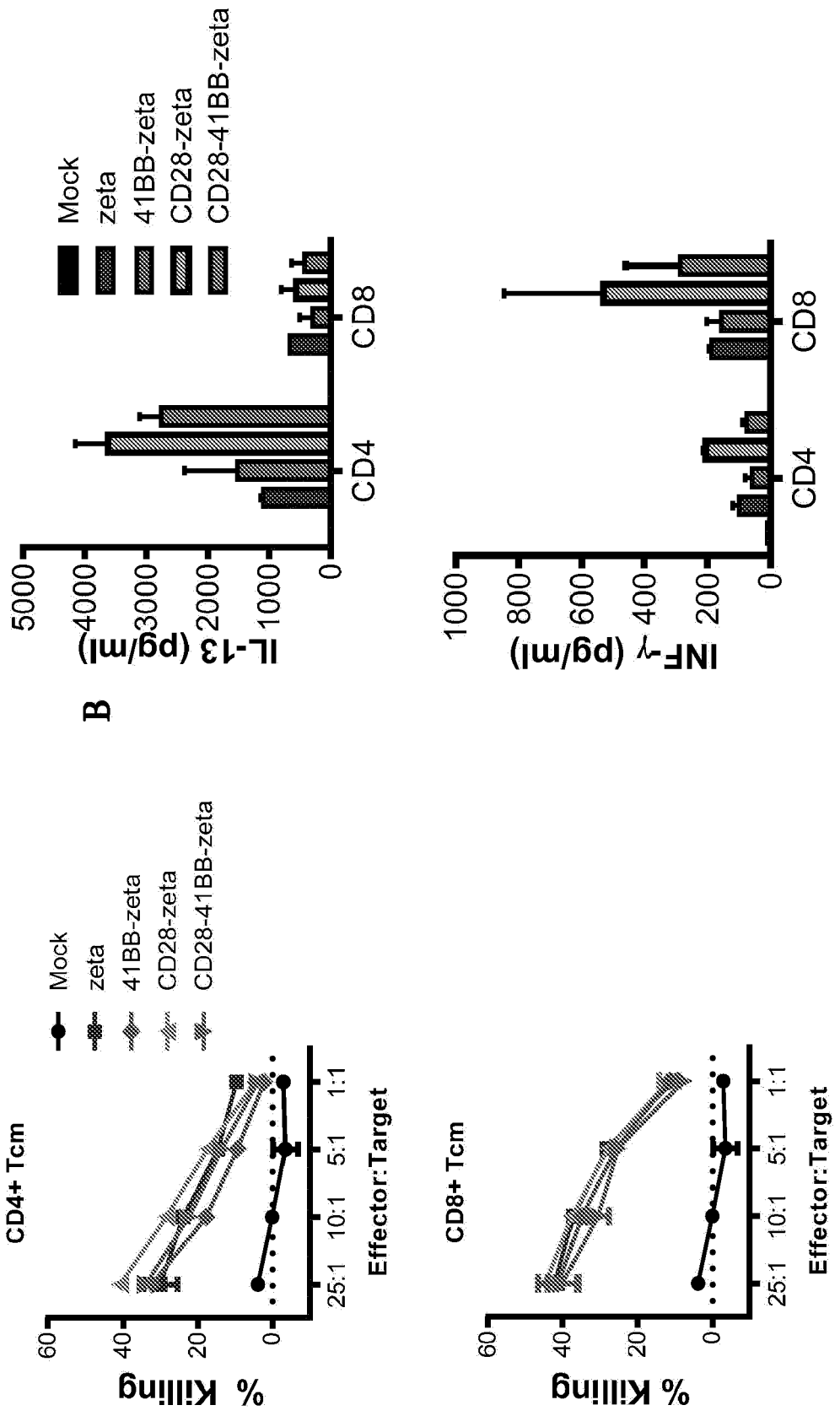

A
CD4+ Tcm
% Killing
Effector:Target
25:1
10:1
5:1
1:1
Mock
zeta
41BB-zeta
CD28-zeta
CD28-41BB-zeta
CD8+ Tcm
B
IL-13 (pg/ml)
INF-γ (pg/ml)
CD4
CD8

FIGURE 15

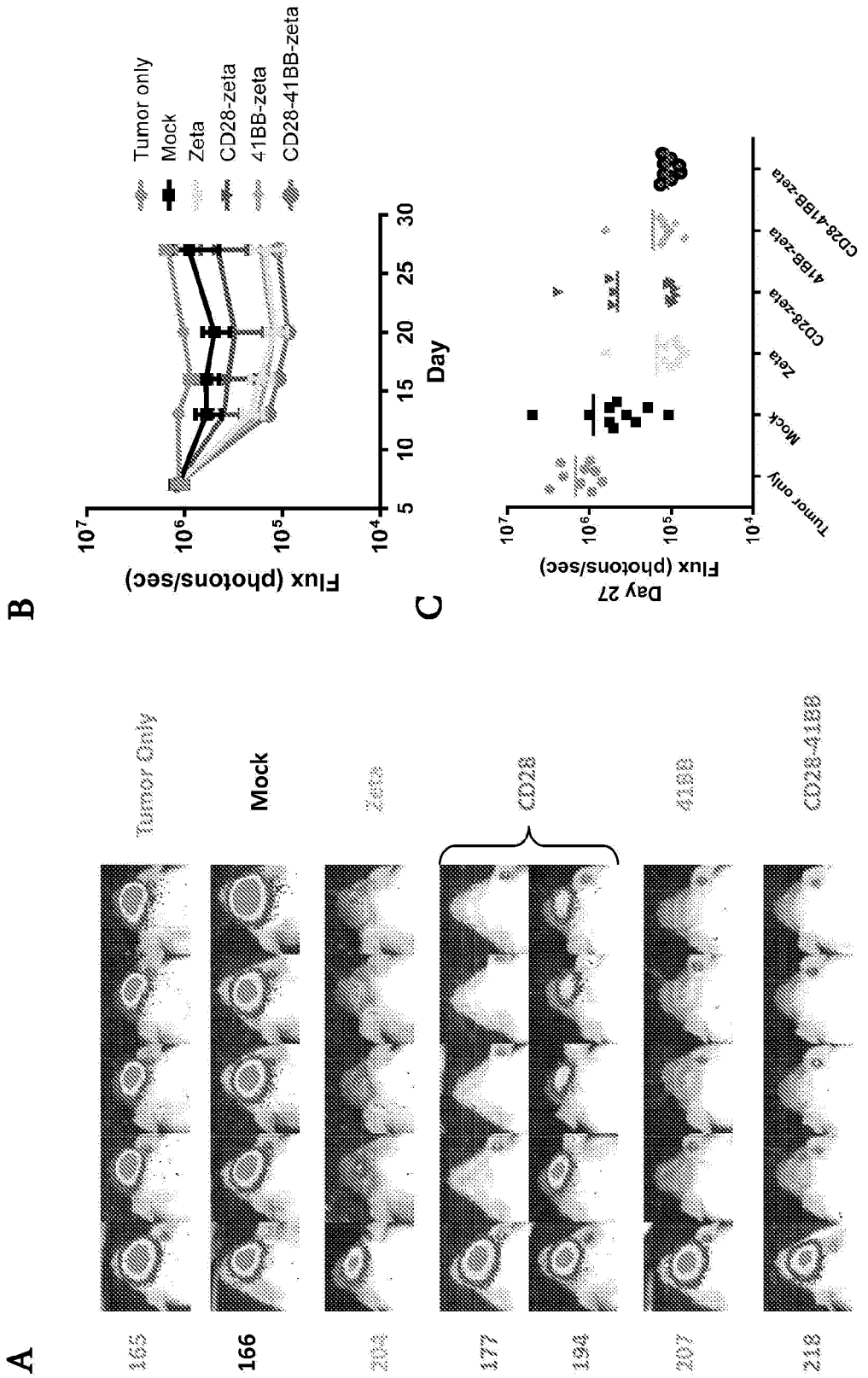

A
Tumor Only
Mock
Zeta
CD28
41BB
CD28-41BB
165
166
204
177
194
207
218
B
Tumor only
Mock
Zeta
CD28-zeta
41BB-zeta
CD28-41BB-zeta
Flux (photons/sec)
Day
C
Day 27
Flux (photons/sec)
Tumor only
Mock
Zeta
CD28-zeta
41BB-zeta
CD28-41BB-zeta

FIGURE 16

FIGURE 17

MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGM

GMCSFRa signal peptide (22 aa) IL13 (112 aa)

YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF

REGRFNESKYGPPCPPCPAPEF**E**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF

IgG4(L235E, N297Q in bold) (229 aa)

NWYVDGVEVHNAKTKPREEQF**Q**STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS

KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKMALIVLGGVAGLL

CD4tm (22 aa)

LFIGLGIFFKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELGGGRVKFSRSADA

41BB (42 aa) Gly3 Zeta (112 aa)

PAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAE

AYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRLEGGGEGRGSLLTCGDV

T2A (24 aa)

EENPGPRMPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLKGTSDGPTQQLTWSRE

CD19t (323 aa)

SPLKPFLKLSLGLPGLGIHMRPLAIWLFIFNVSQQMGGFYLCQPGPPSEKAWQPGWTVNVE

GSGELFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRPEIWEGEPPCVPPR

DSLNQSLSQDLTMAPGSTLWLSCGVPPDSVSRGPLSWTHVHPKGPKSLLSLELKDDRPARD

MWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITARPVLWHWLLRTGGWKVSAVTL

AYLIFCLCSLVGILHLQRALVLRRKR

FIGURE 18

Yellow highlighting indicates the IL-13 optimized codon region including the GMCSF signal sequence (IL13op).
highlighting indicates the IgG4 optimized codon region (IgG4op[L235E, N297Q]).
highlighting indicates the two anticipated amino acid changes within the IgG4 hinge region(L235E and N297Q).
highlighting indicates the CD4 transmembrane optimized codon region.
highlighting indicates the 41BB cytoplasmic signaling region (41BB cyto).
highlighting indicates the 3 glycine linkers (g3).
Gray Highlighting indicates the CD3 zeta optimized codon region (zeta op).
highlighting indicates the T2A sequence (T2A).
highlighting Indicates the truncated CD19 sequence (CD19t).

```
                          1                                                  50
IL13(EQ)41BBZeta      (1) GTTAGACCAGATCTGAGCCTGGGAGCTCTCTGGCTAACTAGGGAACCCAC
 CD19Rop_epHIV7       (1) GTTAGACCAGATCTGAGCCTGGGAGCTCTCTGGCTAACTAGGGAACCCAC
       Consensus      (1) GTTAGACCAGATCTGAGCCTGGGAGCTCTCTGGCTAACTAGGGAACCCAC
                         51                                                 100
IL13(EQ)41BBZeta     (51) TGCTTAAGCCTCAATAAAGCTTGCCTTGAGTGCTTCAAGTAGTGTGTGCC
 CD19Rop_epHIV7      (51) TGCTTAAGCCTCAATAAAGCTTGCCTTGAGTGCTTCAAGTAGTGTGTGCC
       Consensus     (51) TGCTTAAGCCTCAATAAAGCTTGCCTTGAGTGCTTCAAGTAGTGTGTGCC
                        101                                                 150
IL13(EQ)41BBZeta    (101) CGTCTGTTGTGTGACTCTGGTAACTAGAGATCCCTCAGACCCTTTTAGTC
 CD19Rop_epHIV7     (101) CGTCTGTTGTGTGACTCTGGTAACTAGAGATCCCTCAGACCCTTTTAGTC
       Consensus    (101) CGTCTGTTGTGTGACTCTGGTAACTAGAGATCCCTCAGACCCTTTTAGTC
                        151                                                 200
IL13(EQ)41BBZeta    (151) AGTGTGGAAAATCTCTAGCAGTGGCGCCCGAACAGGGACTTGAAAGCGAA
 CD19Rop_epHIV7     (151) AGTGTGGAAAATCTCTAGCAGTGGCGCCCGAACAGGGACTTGAAAGCGAA
       Consensus    (151) AGTGTGGAAAATCTCTAGCAGTGGCGCCCGAACAGGGACTTGAAAGCGAA
                        201                                                 250
IL13(EQ)41BBZeta    (201) AGGGAAACCAGAGGAGCTCTCTCGACGCAGGACTCGGCTTGCTGAAGCGC
 CD19Rop_epHIV7     (201) AGGGAAACCAGAGGAGCTCTCTCGACGCAGGACTCGGCTTGCTGAAGCGC
       Consensus    (201) AGGGAAACCAGAGGAGCTCTCTCGACGCAGGACTCGGCTTGCTGAAGCGC
                        251                                                 300
IL13(EQ)41BBZeta    (251) GCACGGCAAGAGGCGAGGGGCGGCGACTGGTGAGTACGCCAAAAATTTTG
 CD19Rop_epHIV7     (251) GCACGGCAAGAGGCGAGGGGCGGCGACTGGTGAGTACGCCAAAAATTTTG
       Consensus    (251) GCACGGCAAGAGGCGAGGGGCGGCGACTGGTGAGTACGCCAAAAATTTTG
                        301                                                 350
IL13(EQ)41BBZeta    (301) ACTAGCGGAGGCTAGAAGGAGAGAGATGGGTGCGAGAGCGTCAGTATTAA
 CD19Rop_epHIV7     (301) ACTAGCGGAGGCTAGAAGGAGAGAGATGGGTGCGAGAGCGTCAGTATTAA
       Consensus    (301) ACTAGCGGAGGCTAGAAGGAGAGAGATGGGTGCGAGAGCGTCAGTATTAA
                        351                                                 400
IL13(EQ)41BBZeta    (351) GCGGGGGAGAATTAGATCGATGGGAAAAAATTCGGTTAAGGCCAGGGGGA
 CD19Rop_epHIV7     (351) GCGGGGGAGAATTAGATCGATGGGAAAAAATTCGGTTAAGGCCAGGGGGA
       Consensus    (351) GCGGGGGAGAATTAGATCGATGGGAAAAAATTCGGTTAAGGCCAGGGGGA
                        401                                                 450
IL13(EQ)41BBZeta    (401) AAGAAAAAATATAAATTAAAACATATAGTATGGGCAAGCAGGGAGCTAGA
 CD19Rop_epHIV7     (401) AAGAAAAAATATAAATTAAAACATATAGTATGGGCAAGCAGGGAGCTAGA
       Consensus    (401) AAGAAAAAATATAAATTAAAACATATAGTATGGGCAAGCAGGGAGCTAGA
                        451                                                 500
```

```
IL13(EQ)41BBZeta    (451) ACGATTCGCAGTTAATCCTGGCCTGTTAGAAACATCAGAAGGCTGTAGAC
 CD19Rop_epHIV7     (451) ACGATTCGCAGTTAATCCTGGCCTGTTAGAAACATCAGAAGGCTGTAGAC
       Consensus    (451) ACGATTCGCAGTTAATCCTGGCCTGTTAGAAACATCAGAAGGCTGTAGAC
                          501                                             550
IL13(EQ)41BBZeta    (501) AAATACTGGGACAGCTACAACCATCCCTTCAGACAGGATCAGAAGAACTT
 CD19Rop_epHIV7     (501) AAATACTGGGACAGCTACAACCATCCCTTCAGACAGGATCAGAAGAACTT
       Consensus    (501) AAATACTGGGACAGCTACAACCATCCCTTCAGACAGGATCAGAAGAACTT
                          551                                             600
IL13(EQ)41BBZeta    (551) AGATCATTATATAATACAGTAGCAACCCTCTATTGTGTGCATCAAAGGAT
 CD19Rop_epHIV7     (551) AGATCATTATATAATACAGTAGCAACCCTCTATTGTGTGCATCAAAGGAT
       Consensus    (551) AGATCATTATATAATACAGTAGCAACCCTCTATTGTGTGCATCAAAGGAT
                          601                                             650
IL13(EQ)41BBZeta    (601) AGAGATAAAAGACACCAAGGAAGCTTTAGACAAGATAGAGGAAGAGCAAA
 CD19Rop_epHIV7     (601) AGAGATAAAAGACACCAAGGAAGCTTTAGACAAGATAGAGGAAGAGCAAA
       Consensus    (601) AGAGATAAAAGACACCAAGGAAGCTTTAGACAAGATAGAGGAAGAGCAAA
                          651                                             700
IL13(EQ)41BBZeta    (651) ACAAAAGTAAGAAAAAAGCACAGCAAGCAGCAGCTGACACAGGACACAGC
 CD19Rop_epHIV7     (651) ACAAAAGTAAGAAAAAAGCACAGCAAGCAGCAGCTGACACAGGACACAGC
       Consensus    (651) ACAAAAGTAAGAAAAAAGCACAGCAAGCAGCAGCTGACACAGGACACAGC
                          701                                             750
IL13(EQ)41BBZeta    (701) AATCAGGTCAGCCAAAATTACCCTATAGTGCAGAACATCCAGGGGCAAAT
 CD19Rop_epHIV7     (701) AATCAGGTCAGCCAAAATTACCCTATAGTGCAGAACATCCAGGGGCAAAT
       Consensus    (701) AATCAGGTCAGCCAAAATTACCCTATAGTGCAGAACATCCAGGGGCAAAT
                          751                                             800
IL13(EQ)41BBZeta    (751) GGTACATCAGGCCATATCACCTAGAACTTTAAATGCATGGGTAAAAGTAG
 CD19Rop_epHIV7     (751) GGTACATCAGGCCATATCACCTAGAACTTTAAATGCATGGGTAAAAGTAG
       Consensus    (751) GGTACATCAGGCCATATCACCTAGAACTTTAAATGCATGGGTAAAAGTAG
                          801                                             850
IL13(EQ)41BBZeta    (801) TAGAAGAGAAGGCTTTCAGCCCAGAAGTGATACCCATGTTTTCAGCATTA
 CD19Rop_epHIV7     (801) TAGAAGAGAAGGCTTTCAGCCCAGAAGTGATACCCATGTTTTCAGCATTA
       Consensus    (801) TAGAAGAGAAGGCTTTCAGCCCAGAAGTGATACCCATGTTTTCAGCATTA
                          851                                             900
IL13(EQ)41BBZeta    (851) TCAGAAGGAGCCACCCCACAAGATTTAAACACCATGCTAAACACAGTGGG
 CD19Rop_epHIV7     (851) TCAGAAGGAGCCACCCCACAAGATTTAAACACCATGCTAAACACAGTGGG
       Consensus    (851) TCAGAAGGAGCCACCCCACAAGATTTAAACACCATGCTAAACACAGTGGG
                          901                                             950
IL13(EQ)41BBZeta    (901) GGGACATCAAGCAGCCATGCAAATGTTAAAAGAGACCATCAATGAGGAAG
 CD19Rop_epHIV7     (901) GGGACATCAAGCAGCCATGCAAATGTTAAAAGAGACCATCAATGAGGAAG
       Consensus    (901) GGGACATCAAGCAGCCATGCAAATGTTAAAAGAGACCATCAATGAGGAAG
                          951                                            1000
IL13(EQ)41BBZeta    (951) CTGCAGGCAAAGAGAAGAGTGGTGCAGAGAGAAAAAAGAGCAGTGGGAAT
 CD19Rop_epHIV7     (951) CTGCAGGCAAAGAGAAGAGTGGTGCAGAGAGAAAAAAGAGCAGTGGGAAT
       Consensus    (951) CTGCAGGCAAAGAGAAGAGTGGTGCAGAGAGAAAAAAGAGCAGTGGGAAT
                         1001                                            1050
IL13(EQ)41BBZeta   (1001) AGGAGCTTTGTTCCTTGGGTTCTTGGGAGCAGCAGGAAGCACTATGGGCG
 CD19Rop_epHIV7    (1001) AGGAGCTTTGTTCCTTGGGTTCTTGGGAGCAGCAGGAAGCACTATGGGCG
       Consensus   (1001) AGGAGCTTTGTTCCTTGGGTTCTTGGGAGCAGCAGGAAGCACTATGGGCG
                         1051                                            1100
IL13(EQ)41BBZeta   (1051) CAGCGTCAATGACGCTGACGGTACAGGCCAGACAATTATTGTCTGGTATA
 CD19Rop_epHIV7    (1051) CAGCGTCAATGACGCTGACGGTACAGGCCAGACAATTATTGTCTGGTATA
       Consensus   (1051) CAGCGTCAATGACGCTGACGGTACAGGCCAGACAATTATTGTCTGGTATA
                         1101                                            1150
IL13(EQ)41BBZeta   (1101) GTGCAGCAGCAGAACAATTTGCTGAGGGCTATTGAGGCGCAACAGCATCT
 CD19Rop_epHIV7    (1101) GTGCAGCAGCAGAACAATTTGCTGAGGGCTATTGAGGCGCAACAGCATCT
       Consensus   (1101) GTGCAGCAGCAGAACAATTTGCTGAGGGCTATTGAGGCGCAACAGCATCT
```

```
                          1151                                                1200
IL13(EQ)41BBZeta  (1151) GTTGCAACTCACAGTCTGGGGCATCAAGCAGCTCCAGGCAAGAATCCTGG
 CD19Rop_epHIV7   (1151) GTTGCAACTCACAGTCTGGGGCATCAAGCAGCTCCAGGCAAGAATCCTGG
       Consensus  (1151) GTTGCAACTCACAGTCTGGGGCATCAAGCAGCTCCAGGCAAGAATCCTGG
                          1201                                                1250
IL13(EQ)41BBZeta  (1201) CTGTGGAAAGATACCTAAAGGATCAACAGCTCCTGGGGATTTGGGGTTGC
 CD19Rop_epHIV7   (1201) CTGTGGAAAGATACCTAAAGGATCAACAGCTCCTGGGGATTTGGGGTTGC
       Consensus  (1201) CTGTGGAAAGATACCTAAAGGATCAACAGCTCCTGGGGATTTGGGGTTGC
                          1251                                                1300
IL13(EQ)41BBZeta  (1251) TCTGGAAAACTCATTTGCACCACTGCTGTGCCTTGGATCTACAAATGGCA
 CD19Rop_epHIV7   (1251) TCTGGAAAACTCATTTGCACCACTGCTGTGCCTTGGATCTACAAATGGCA
       Consensus  (1251) TCTGGAAAACTCATTTGCACCACTGCTGTGCCTTGGATCTACAAATGGCA
                          1301                                                1350
IL13(EQ)41BBZeta  (1301) GTATTCATCCACAATTTTAAAAGAAAAGGGGGGATTGGGGGGTACAGTGC
 CD19Rop_epHIV7   (1301) GTATTCATCCACAATTTTAAAAGAAAAGGGGGGATTGGGGGGTACAGTGC
       Consensus  (1301) GTATTCATCCACAATTTTAAAAGAAAAGGGGGGATTGGGGGGTACAGTGC
                          1351                                                1400
IL13(EQ)41BBZeta  (1351) AGGGGAAAGAATAGTAGACATAATAGCAACAGACATACAAACTAAAGAAT
 CD19Rop_epHIV7   (1351) AGGGGAAAGAATAGTAGACATAATAGCAACAGACATACAAACTAAAGAAT
       Consensus  (1351) AGGGGAAAGAATAGTAGACATAATAGCAACAGACATACAAACTAAAGAAT
                          1401                                                1450
IL13(EQ)41BBZeta  (1401) TACAAAAACAAATTACAAAAATTCAAAATTTTCGGGTTTATTACAGGGAC
 CD19Rop_epHIV7   (1401) TACAAAAACAAATTACAAAAATTCAAAATTTTCGGGTTTATTACAGGGAC
       Consensus  (1401) TACAAAAACAAATTACAAAAATTCAAAATTTTCGGGTTTATTACAGGGAC
                          1451                                                1500
IL13(EQ)41BBZeta  (1451) AGCAGAGATCCAGTTTGGGGATCAATTGCATGAAGAATCTGCTTAGGGTT
 CD19Rop_epHIV7   (1451) AGCAGAGATCCAGTTTGGGGATCAATTGCATGAAGAATCTGCTTAGGGTT
       Consensus  (1451) AGCAGAGATCCAGTTTGGGGATCAATTGCATGAAGAATCTGCTTAGGGTT
                          1501                                                1550
IL13(EQ)41BBZeta  (1501) AGGCGTTTTGCGCTGCTTCGCGAGGATCTGCGATCGCTCCGGTGCCCGTC
 CD19Rop_epHIV7   (1501) AGGCGTTTTGCGCTGCTTCGCGAGGATCTGCGATCGCTCCGGTGCCCGTC
       Consensus  (1501) AGGCGTTTTGCGCTGCTTCGCGAGGATCTGCGATCGCTCCGGTGCCCGTC
                          1551                                                1600
IL13(EQ)41BBZeta  (1551) AGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGGGGGAGGG
 CD19Rop_epHIV7   (1551) AGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGGGGGAGGG
       Consensus  (1551) AGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGGGGGAGGG
                          1601                                                1650
IL13(EQ)41BBZeta  (1601) GTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGA
 CD19Rop_epHIV7   (1601) GTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGA
       Consensus  (1601) GTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGA
                          1651                                                1700
IL13(EQ)41BBZeta  (1651) AAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAAC
 CD19Rop_epHIV7   (1651) AAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAAC
       Consensus  (1651) AAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAAC
                          1701                                                1750
IL13(EQ)41BBZeta  (1701) CGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTT
 CD19Rop_epHIV7   (1701) CGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTT
       Consensus  (1701) CGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTT
                          1751                                                1800
IL13(EQ)41BBZeta  (1751) GCCGCCAGAACACAGCTGAAGCTTCGAGGGGCTCGCATCTCTCCTTCACG
 CD19Rop_epHIV7   (1751) GCCGCCAGAACACAGCTGAAGCTTCGAGGGGCTCGCATCTCTCCTTCACG
       Consensus  (1751) GCCGCCAGAACACAGCTGAAGCTTCGAGGGGCTCGCATCTCTCCTTCACG
                          1801                                                1850
IL13(EQ)41BBZeta  (1801) CGCCCGCCGCCCTACCTGAGGCCGCCATCCACGCCGGTTGAGTCGCGTTC
 CD19Rop_epHIV7   (1801) CGCCCGCCGCCCTACCTGAGGCCGCCATCCACGCCGGTTGAGTCGCGTTC
```

```
       Consensus  (1801) CGCCCGCCGCCCTACCTGAGGCCGCCATCCACGCCGGTTGAGTCGCGTTC
                         1851                                          1900
IL13(EQ)41BBZeta  (1851) TGCCGCCTCCCGCCTGTGGTGCCTCCTGAACTGCGTCCGCCGTCTAGGTA
 CD19Rop_epHIV7   (1851) TGCCGCCTCCCGCCTGTGGTGCCTCCTGAACTGCGTCCGCCGTCTAGGTA
       Consensus  (1851) TGCCGCCTCCCGCCTGTGGTGCCTCCTGAACTGCGTCCGCCGTCTAGGTA
                         1901                                          1950
IL13(EQ)41BBZeta  (1901) AGTTTAAAGCTCAGGTCGAGACCGGGCCTTTGTCCGGCGCTCCCTTGGAG
 CD19Rop_epHIV7   (1901) AGTTTAAAGCTCAGGTCGAGACCGGGCCTTTGTCCGGCGCTCCCTTGGAG
       Consensus  (1901) AGTTTAAAGCTCAGGTCGAGACCGGGCCTTTGTCCGGCGCTCCCTTGGAG
                         1951                                          2000
IL13(EQ)41BBZeta  (1951) CCTACCTAGACTCAGCCGGCTCTCCACGCTTTGCCTGACCCTGCTTGCTC
 CD19Rop_epHIV7   (1951) CCTACCTAGACTCAGCCGGCTCTCCACGCTTTGCCTGACCCTGCTTGCTC
       Consensus  (1951) CCTACCTAGACTCAGCCGGCTCTCCACGCTTTGCCTGACCCTGCTTGCTC
                         2001                                          2050
IL13(EQ)41BBZeta  (2001) AACTCTACGTCTTTGTTTCGTTTTCTGTTCTGCGCCGTTACAGATCCAAG
 CD19Rop_epHIV7   (2001) AACTCTACGTCTTTGTTTCGTTTTCTGTTCTGCGCCGTTACAGATCCAAG
       Consensus  (2001) AACTCTACGTCTTTGTTTCGTTTTCTGTTCTGCGCCGTTACAGATCCAAG
                         2051                                          2100
IL13(EQ)41BBZeta  (2051) CTGTGACCGGCGCCTACGGCTAGCGCCGCCACCATGCTGCTGCTGGTGAC
 CD19Rop_epHIV7   (2051) CTGTGACCGGCGCCTACGGCTAGCGCCGCCACCATGCTGCTGCTGGTGAC
       Consensus  (2051) CTGTGACCGGCGCCTACGGCTAGCGCCGCCACCATGCTGCTGCTGGTGAC
                         2101                                          2150
IL13(EQ)41BBZeta  (2101) CAGCCTGCTGCTGTGCGAGCTGCCCCACCCCGCCTTTCTGCTGATCCCTG
 CD19Rop_epHIV7   (2101) CAGCCTGCTGCTGTGCGAGCTGCCCCACCCCGCCTTTCTGCTGATCCCCG
       Consensus  (2101) CAGCCTGCTGCTGTGCGAGCTGCCCCACCCCGCCTTTCTGCTGATCCC G
                         2151                                          2200
IL13(EQ)41BBZeta  (2151) GC--CCCG-TGCCCCCTAGCACCGCC---CTGCGCTACCTGATCGAGGAA
 CD19Rop_epHIV7   (2151) ACATCCAGATGACCCAGACCACCTCCAGCCTGAGCGCCAGCCTGGGCGAC
       Consensus  (2151)  C  CC G TG CCC  A CACC CC   CTG GC  C    T G  GA
                         2201                                          2250
IL13(EQ)41BBZeta  (2195) CTGGTGA------------------------ACATCACCCAGAACCAGAA
 CD19Rop_epHIV7   (2201) CGGGTGACCATCAGCTGCCGGGCCAGCCAGGACATCAGCAAGTACCTGAA
       Consensus  (2201) C GGTGA                        ACATCA C AG ACC GAA
                         2251                                          2300
IL13(EQ)41BBZeta  (2221) --------------AGCCC-------CC---------CTGTGCAAC----
 CD19Rop_epHIV7   (2251) CTGGTATCAGCAGAAGCCCGACGGCACCGTCAAGCTGCTGATCTACCACA
       Consensus  (2251)               AGCCC       CC         CTG  C AC
                         2301                                          2350
IL13(EQ)41BBZeta  (2237) ------GGCAGCAT---GGTGTG---------------------------
 CD19Rop_epHIV7   (2301) CCAGCCGGCTGCACAGCGGCGTGCCCAGCCGGTTTAGCGGCAGCGGCTCC
       Consensus  (2301)       GGC GCA    GG GTG
                         2351                                          2400
IL13(EQ)41BBZeta  (2251) -----------------GAGCATC---AACCTG-----------------
 CD19Rop_epHIV7   (2351) GGCACCGACTACAGCCTGACCATCTCCAACCTGGAACAGGAAGATATCGC
       Consensus  (2351)                   GA CATC   AACCTG
                         2401                                          2450
IL13(EQ)41BBZeta  (2264) -ACC-------GCCGGCATGT------ACTG-----------TGCCGCC-
 CD19Rop_epHIV7   (2401) CACCTACTTTTGCCAGCAGGGCAACACACTGCCCTACACCTTTGGCGGCG
       Consensus  (2401)  ACC       GCC GCA G       ACTG           TG CG C
                         2451                                          2500
IL13(EQ)41BBZeta  (2288) --------CTGGAAA------GCCTGATCAACGTGAGCGGCT--------
 CD19Rop_epHIV7   (2451) GAACAAAGCTGGAAATCACCGGCAGCACCTCCGGCAGCGGCAAGCCTGGC
       Consensus  (2451)         CTGGAAA      GC   A C  CG  AGCGGC
                         2501                                          2550
IL13(EQ)41BBZeta  (2316) ----------GCAGCGCCATCG--------------AGAAAA-------
```

```
 CD19Rop_epHIV7   (2501) AGCGGCGAGGGCAGCACCAAGGGCGAGGTGAAGCTGCAGGAAAGCGGCCC
       Consensus  (2501)           GCAGC CCA  G               AG AAA
                         2551                                          2600
IL13(EQ)41BBZeta  (2334) -------------CCCAGCG------------------------------
 CD19Rop_epHIV7   (2551) TGGCCTGGTGGCCCCCAGCCAGAGCCTGAGCGTGACCTGCACCGTGAGCG
       Consensus  (2551)              CCCAGC
                         2601                                          2650
IL13(EQ)41BBZeta  (2341) ----GATGCTGTCCGGCTTCTGC------------------CCCCACAAG
 CD19Rop_epHIV7   (2601) GCGTGAGCCTGCCCGACTACGGCGTGAGCTGGATCCGGCAGCCCCCCAGG
       Consensus  (2601)     GA  CTG CCG CT C GC                   CCCC CA G
                         2651                                          2700
IL13(EQ)41BBZeta  (2369) ----------------------------GTGTCCGCCGGAC-----AGTT
 CD19Rop_epHIV7   (2651) AAGGGCCTGGAATGGCTGGGCGTGATCTGGGGCAGCGAGACCACCTACTA
       Consensus  (2651)                               G G C GC  GAC     A T
                         2701                                          2750
IL13(EQ)41BBZeta  (2386) CAGCAGCCTGC--ACGTGCGGG------------------ACACCAAGA
 CD19Rop_epHIV7   (2701) CAACAGCGCCCTGAAGAGCCGGCTGACCATCATCAAGGACAACAGCAAGA
       Consensus  (2701) CA CAGC   C  A G GC GG                    ACA CAAGA
                         2751                                          2800
IL13(EQ)41BBZeta  (2415) TCGAGGTGGCCCAGTTCGTGAAGGACCTGCTG-----------------C
 CD19Rop_epHIV7   (2751) GCCAGGTGTTCCTGAAGATGAACAGCCTGCAGACCGACGACACCGCCATC
       Consensus  (2751)  C AGGTG  CC G    TGAA   CCTGC G                 C
                         2801                                          2850
IL13(EQ)41BBZeta  (2448) TGCACCTG----AAGAA--------------GCTGTTCCG----GGA---
 CD19Rop_epHIV7   (2801) TACTACTGCGCCAAGCACTACTACTACGGCGGCAGCTACGCCATGGACTA
       Consensus  (2801) T C  CTG    AAG A              GC G T CG    GGA
                         2851                                          2900
IL13(EQ)41BBZeta  (2473) ---GGGCCGGTTCAAC------------------
 CD19Rop_epHIV7   (2851) CTGGGGCCAGGGCACCAGCGTGACCGTGAGCAGCGAGAGCAAGTACGGCC
       Consensus  (2851)    GGGCC G  CA C                  GAGAGCAAGTACGGCC
                         2901                                          2950
IL13(EQ)41BBZeta  (2502)
 CD19Rop_epHIV7   (2901) CTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCCTGGGCGGACCCAGCGTG
       Consensus  (2901) CTCCCTGCCCCCCTTGCCCTGCCCC GAGTTC  GGGCGGACCCAGCGTG
                         2951                                          3000
IL13(EQ)41BBZeta  (2552)
 CD19Rop_epHIV7   (2951) TTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCCGGACCCC
       Consensus  (2951) TTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCCGGACCCC
                         3001                                          3050
IL13(EQ)41BBZeta  (2602)
 CD19Rop_epHIV7   (3001) CGAGGTGACCTGCGTGGTGGTGGACGTGAGCCAGGAAGATCCCGAGGTCC
       Consensus  (3001)  GAGGTGACCTGCGTGGTGGTGGACGTGAGCCAGGAAGATCC GAGGTCC
                         3051                                          3100
IL13(EQ)41BBZeta  (2652)
 CD19Rop_epHIV7   (3051) AGTTCAATTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAG
       Consensus  (3051) AGTTCAATTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAG
                         3101                                          3150
IL13(EQ)41BBZeta  (2702)
 CD19Rop_epHIV7   (3101) CCCAGGGAAGAGCAGTTCAACAGCACCTACCGGGTGGTGTCCGTGCTGAC
       Consensus  (3101) CCCAGGGAAGAGCAGTTC A AGCACCTACCGGGTGGTGTCCGTGCTGAC
                         3151                                          3200
IL13(EQ)41BBZeta  (2752)
 CD19Rop_epHIV7   (3151) CGTGCTGCACCAGGACTGGCTGAACGGCAAAGAATACAAGTGCAAGGTGT
       Consensus  (3151) CGTGCTGCACCAGGACTGGCTGAACGGCAAAGAATACAAGTGCAAGGTGT
                         3201                                          3250
```

```
IL13(EQ)41BBZeta  (2802)
 CD19Rop_epHIV7   (3201) CCAACAAGGGCCTGCCCAGCAGCATCGAGAAAACCATCAGCAAGGCCAAG
       Consensus  (3201) CCAACAAGGGCCTGCCCAGCAGCATCGAGAAAACCATCAGCAAGGCCAAG
                         3251                                          3300
IL13(EQ)41BBZeta  (2852)
 CD19Rop_epHIV7   (3251) GGCCAGCCTCGGGAGCCCCAGGTGTACACCCTGCCCCCTTCCCAGGAAGA
       Consensus  (3251) GGCCAGCCTCGGGAGCCCCAGGTGTACACCCTGCCCCCTTCCCAGGAAGA
                         3301                                          3350
IL13(EQ)41BBZeta  (2902)
 CD19Rop_epHIV7   (3301) GATGACCAAGAATCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACC
       Consensus  (3301) GATGACCAAGAATCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACC
                         3351                                          3400
IL13(EQ)41BBZeta  (2952)
 CD19Rop_epHIV7   (3351) CCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAAC
       Consensus  (3351) CCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAAC
                         3401                                          3450
IL13(EQ)41BBZeta  (3002) TACAAGACCACCCCCCCTGTGCTGGACAGCGACGGCAGCTTCTTCCTGTA
 CD19Rop_epHIV7   (3401) TACAAGACCACCCCCCCTGTGCTGGACAGCGACGGCAGCTTCTTCCTGTA
       Consensus  (3401) TACAAGACCACCCCCCCTGTGCTGGACAGCGACGGCAGCTTCTTCCTGTA
                         3451                                          3500
IL13(EQ)41BBZeta  (3052) CAGCAGGCTGACCGTGGACAAGAGCCGGTGGCAGGAAGGCAACGTCTTTA
 CD19Rop_epHIV7   (3451) CAGCAGGCTGACCGTGGACAAGAGCCGGTGGCAGGAAGGCAACGTCTTTA
       Consensus  (3451) CAGCAGGCTGACCGTGGACAAGAGCCGGTGGCAGGAAGGCAACGTCTTTA
                         3501                                          3550
IL13(EQ)41BBZeta  (3102) GCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGC
 CD19Rop_epHIV7   (3501) GCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGC
       Consensus  (3501) GCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGC
                         3551                                          3600
IL13(EQ)41BBZeta  (3152) CTGTCCCTGAGCCTGGGCAAG
 CD19Rop_epHIV7   (3551) CTGTCCCTGAGCCTGGGCAAGATGGCCCTGATCGTGCTGGGCGGCGTGGC
       Consensus  (3551) CTGTCCCTGAGCCTGGGCAAGATGGCCCTGATCGTGCTGGGCGGCGTGGC
                         3601                                          3650
IL13(EQ)41BBZeta  (3202)
 CD19Rop_epHIV7   (3601) CGGGCTGCTGCTGTTCATCGGCCTGGGCATCTTTTTC-------------
       Consensus  (3601) CGGGCTGCTGCTGTTCATCGGCCTGGGCATCTTTTTC
                         3651                                          3700
IL13(EQ)41BBZeta  (3252)
 CD19Rop_epHIV7   (3638) ----------------------------C----------------------
       Consensus  (3651)                             C
                         3701                                          3750
IL13(EQ)41BBZeta  (3302)
 CD19Rop_epHIV7   (3639) --------------------------------------------------
       Consensus  (3701)
                         3751                                          3800
IL13(EQ)41BBZeta  (3352)                       CGGGTGAAGTTCAGCCGGTCCGCCGACG
 CD19Rop_epHIV7   (3639) ----------------------GGGTGAAGTTCAGCCGGTCCGCCGACG
       Consensus  (3751)                        GGGTGAAGTTCAGCCGGTCCGCCGACG
                         3801                                          3850
IL13(EQ)41BBZeta  (3402) CCCCTGCCTACCAGCAGGGCCAGAACCAGCTGTACAACGAGCTGAACCTG
 CD19Rop_epHIV7   (3666) CCCCTGCCTACCAGCAGGGCCAGAACCAGCTGTACAACGAGCTGAACCTG
       Consensus  (3801) CCCCTGCCTACCAGCAGGGCCAGAACCAGCTGTACAACGAGCTGAACCTG
                         3851                                          3900
IL13(EQ)41BBZeta  (3452) GGCAGGCGGGAGGAATACGACGTGCTGGACAAGCGGAGAGGCCGGGACCC
 CD19Rop_epHIV7   (3716) GGCAGGCGGGAGGAATACGACGTGCTGGACAAGCGGAGAGGCCGGGACCC
       Consensus  (3851) GGCAGGCGGGAGGAATACGACGTGCTGGACAAGCGGAGAGGCCGGGACCC
```

```
                          3901                                                 3950
IL13(EQ)41BBZeta  (3502) TGAGATGGGCGGCAAGCCTCGGCGGAAGAACCCCCAGGAAGGCCTGTATA
 CD19Rop_epHIV7   (3766) TGAGATGGGCGGCAAGCCCAGGCGGAAGAACCCTCAGGAAGGCCTGTATA
       Consensus  (3901) TGAGATGGGCGGCAAGCC  GGCGGAAGAACCC CAGGAAGGCCTGTATA
                          3951                                                 4000
IL13(EQ)41BBZeta  (3552) ACGAACTGCAGAAAGACAAGATGGCCGAGGCCTACAGCGAGATCGGCATG
 CD19Rop_epHIV7   (3816) ACGAACTGCAGAAAGACAAGATGGCCGAGGCCTACAGCGAGATCGGCATG
       Consensus  (3951) ACGAACTGCAGAAAGACAAGATGGCCGAGGCCTACAGCGAGATCGGCATG
                          4001                                                 4050
IL13(EQ)41BBZeta  (3602) AAGGGCGAGCGGAGGCGGGGCAAGGGCCACGACGGCCTGTATCAGGGCCT
 CD19Rop_epHIV7   (3866) AAGGGCGAGCGGCGGAGGGGCAAGGGCCACGACGGCCTGTACCAGGGCCT
       Consensus  (4001) AAGGGCGAGCGG GG GGGGCAAGGGCCACGACGGCCTGTA CAGGGCCT
                          4051                                                 4100
IL13(EQ)41BBZeta  (3652) GTCCACCGCCACCAAGGATACCTACGACGCCCTGCACATGCAGGCCCTGC
 CD19Rop_epHIV7   (3916) GAGCACCGCCACCAAGGATACCTACGACGCCCTGCACATGCAGGCCCTGC
       Consensus  (4051) G  CACCGCCACCAAGGATACCTACGACGCCCTGCACATGCAGGCCCTGC
                          4101                                                 4150
IL13(EQ)41BBZeta  (3702) CCCCAAGG
 CD19Rop_epHIV7   (3966) CCCC----------------------------------------------
       Consensus  (4101) CCCC
                          4151                                                 4200
IL13(EQ)41BBZeta  (3752)
 CD19Rop_epHIV7   (3970) ----------------------------------------------------
       Consensus  (4151)
                          4201                                                 4250
IL13(EQ)41BBZeta  (3802)
 CD19Rop_epHIV7   (3970) ----------------------------------------------------
       Consensus  (4201)
                          4251                                                 4300
IL13(EQ)41BBZeta  (3852)
 CD19Rop_epHIV7   (3970) ----------------------------------------------------
       Consensus  (4251)
                          4301                                                 4350
IL13(EQ)41BBZeta  (3902)
 CD19Rop_epHIV7   (3970) ----------------------------------------------------
       Consensus  (4301)
                          4351                                                 4400
IL13(EQ)41BBZeta  (3952)
 CD19Rop_epHIV7   (3970) ----------------------------------------------------
       Consensus  (4351)
                          4401                                                 4450
IL13(EQ)41BBZeta  (4002)
 CD19Rop_epHIV7   (3970) ----------------------------------------------------
       Consensus  (4401)
                          4451                                                 4500
IL13(EQ)41BBZeta  (4052)
 CD19Rop_epHIV7   (3970) ----------------------------------------------------
       Consensus  (4451)
                          4501                                                 4550
IL13(EQ)41BBZeta  (4102)
 CD19Rop_epHIV7   (3970) ----------------------------------------------------
       Consensus  (4501)
                          4551                                                 4600
IL13(EQ)41BBZeta  (4152)
 CD19Rop_epHIV7   (3970) ----------------------------------------------------
```

```
       Consensus  (4551)
                         4601                                                4650
IL13(EQ)41BBZeta  (4202)
 CD19Rop_epHIV7   (3970) --------------------------------------------------
       Consensus  (4601)
                         4651                                                4700
IL13(EQ)41BBZeta  (4252)
 CD19Rop_epHIV7   (3970) --------------------------------------------------
       Consensus  (4651)
                         4701                                                4750
IL13(EQ)41BBZeta  (4302)
 CD19Rop_epHIV7   (3970) ------------------------------C------AGG-----------
       Consensus  (4701)                                C      AGG
                         4751                                                4800
IL13(EQ)41BBZeta  (4352)
 CD19Rop_epHIV7   (3974) --------------------------------T-----------------
       Consensus  (4751)
                         4801                                                4850
IL13(EQ)41BBZeta  (4402)
 CD19Rop_epHIV7   (3975) --------------------------------------------------
       Consensus  (4801)
                         4851                                                4900
IL13(EQ)41BBZeta  (4452)
 CD19Rop_epHIV7   (3975) --------------------------------------------------
       Consensus  (4851)
                         4901                                                4950
IL13(EQ)41BBZeta  (4502)
 CD19Rop_epHIV7   (3975) --------------------------------------------------
       Consensus  (4901)
                         4951                                                5000
IL13(EQ)41BBZeta  (4552)
 CD19Rop_epHIV7   (3975) --------------------------------------------------
       Consensus  (4951)
                         5001                                                5050
IL13(EQ)41BBZeta  (4602)
 CD19Rop_epHIV7   (3975) --------------------------------------------------
       Consensus  (5001)
                         5051                                                5100
IL13(EQ)41BBZeta  (4652)
 CD19Rop_epHIV7   (3975) --------------------------------------------------
       Consensus  (5051)
                         5101                                                5150
IL13(EQ)41BBZeta  (4702)
 CD19Rop_epHIV7   (3975) --------------------------------------------------
       Consensus  (5101)
                         5151                                                5200
IL13(EQ)41BBZeta  (4752)   TCTAGACCCGGGCTGCAGGAATTCGATATCAAGCTTATCGATAATCAA
 CD19Rop_epHIV7   (3975) ------GACCCGGGCTGCAGGAATTCGATATCAAGCTTATCGATAATCAA
       Consensus  (5151)       GACCCGGGCTGCAGGAATTCGATATCAAGCTTATCGATAATCAA
                         5201                                                5250
IL13(EQ)41BBZeta  (4802) CCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGT
 CD19Rop_epHIV7   (4019) CCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGT
       Consensus  (5201) CCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGT
                         5251                                                5300
IL13(EQ)41BBZeta  (4852) TGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATG
```

```
CD19Rop_epHIV7   (4069) TGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATG
      Consensus  (5251) TGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATG
                        5301                                          5350
IL13(EQ)41BBZeta (4902) CTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGG
CD19Rop_epHIV7   (4119) CTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGG
      Consensus  (5301) CTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGG
                        5351                                          5400
IL13(EQ)41BBZeta (4952) TTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGT
CD19Rop_epHIV7   (4169) TTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGT
      Consensus  (5351) TTGCTGTCTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGT
                        5401                                          5450
IL13(EQ)41BBZeta (5002) GGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGCCA
CD19Rop_epHIV7   (4219) GGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGCCA
      Consensus  (5401) GGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGCCA
                        5451                                          5500
IL13(EQ)41BBZeta (5052) CCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCC
CD19Rop_epHIV7   (4269) CCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCC
      Consensus  (5451) CCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCC
                        5501                                          5550
IL13(EQ)41BBZeta (5102) ACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCG
CD19Rop_epHIV7   (4319) ACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCG
      Consensus  (5501) ACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCG
                        5551                                          5600
IL13(EQ)41BBZeta (5152) GCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCT
CD19Rop_epHIV7   (4369) GCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCT
      Consensus  (5551) GCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCT
                        5601                                          5650
IL13(EQ)41BBZeta (5202) TTCCTTGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCC
CD19Rop_epHIV7   (4419) TTCCTTGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCC
      Consensus  (5601) TTCCTTGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCC
                        5651                                          5700
IL13(EQ)41BBZeta (5252) TTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGG
CD19Rop_epHIV7   (4469) TTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGG
      Consensus  (5651) TTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGG
                        5701                                          5750
IL13(EQ)41BBZeta (5302) CCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGA
CD19Rop_epHIV7   (4519) CCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGA
      Consensus  (5701) CCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGA
                        5751                                          5800
IL13(EQ)41BBZeta (5352) CGAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCATCGATACCGTCGACTA
CD19Rop_epHIV7   (4569) CGAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCATCGATACCGTCGACTA
      Consensus  (5751) CGAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCATCGATACCGTCGACTA
                        5801                                          5850
IL13(EQ)41BBZeta (5402) GCCGTACCTTTAAGACCAATGACTTACAAGGCAGCTGTAGATCTTAGCCA
CD19Rop_epHIV7   (4619) GCCGTACCTTTAAGACCAATGACTTACAAGGCAGCTGTAGATCTTAGCCA
      Consensus  (5801) GCCGTACCTTTAAGACCAATGACTTACAAGGCAGCTGTAGATCTTAGCCA
                        5851                                          5900
IL13(EQ)41BBZeta (5452) CTTTTTAAAAGAAAAGGGGGGACTGGAAGGGCTAATTCACTCCCAAAGAA
CD19Rop_epHIV7   (4669) CTTTTTAAAAGAAAAGGGGGGACTGGAAGGGCTAATTCACTCCCAAAGAA
      Consensus  (5851) CTTTTTAAAAGAAAAGGGGGGACTGGAAGGGCTAATTCACTCCCAAAGAA
                        5901                                          5950
IL13(EQ)41BBZeta (5502) GACAAGATCTGCTTTTTGCCTGTACTGGGTCTCTCTGGTTAGACCAGATC
CD19Rop_epHIV7   (4719) GACAAGATCTGCTTTTTGCCTGTACTGGGTCTCTCTGGTTAGACCAGATC
      Consensus  (5901) GACAAGATCTGCTTTTTGCCTGTACTGGGTCTCTCTGGTTAGACCAGATC
                        5951                                          6000
```

```
IL13(EQ)41BBZeta  (5552) TGAGCCTGGGAGCTCTCTGGCTAACTAGGGAACCCACTGCTTAAGCCTCA
 CD19Rop_epHIV7   (4769) TGAGCCTGGGAGCTCTCTGGCTAACTAGGGAACCCACTGCTTAAGCCTCA
       Consensus  (5951) TGAGCCTGGGAGCTCTCTGGCTAACTAGGGAACCCACTGCTTAAGCCTCA
                         6001                                          6050
IL13(EQ)41BBZeta  (5602) ATAAAGCTTGCCTTGAGTGCTTCAAGTAGTGTGTGCCCGTCTGTTGTGTG
 CD19Rop_epHIV7   (4819) ATAAAGCTTGCCTTGAGTGCTTCAAGTAGTGTGTGCCCGTCTGTTGTGTG
       Consensus  (6001) ATAAAGCTTGCCTTGAGTGCTTCAAGTAGTGTGTGCCCGTCTGTTGTGTG
                         6051                                          6100
IL13(EQ)41BBZeta  (5652) ACTCTGGTAACTAGAGATCCCTCAGACCCTTTTAGTCAGTGTGGAAAATC
 CD19Rop_epHIV7   (4869) ACTCTGGTAACTAGAGATCCCTCAGACCCTTTTAGTCAGTGTGGAAAATC
       Consensus  (6051) ACTCTGGTAACTAGAGATCCCTCAGACCCTTTTAGTCAGTGTGGAAAATC
                         6101                                          6150
IL13(EQ)41BBZeta  (5702) TCTAGCAGAATTCGATATCAAGCTTATCGATACCGTCGACCTCGAGGGGG
 CD19Rop_epHIV7   (4919) TCTAGCAGAATTCGATATCAAGCTTATCGATACCGTCGACCTCGAGGGGG
       Consensus  (6101) TCTAGCAGAATTCGATATCAAGCTTATCGATACCGTCGACCTCGAGGGGG
                         6151                                          6200
IL13(EQ)41BBZeta  (5752) GGCCCGGTACCCAATTCGCCCTATAGTGAGTCGTATTACAATTCACTGGC
 CD19Rop_epHIV7   (4969) GGCCCGGTACCCAATTCGCCCTATAGTGAGTCGTATTACAATTCACTGGC
       Consensus  (6151) GGCCCGGTACCCAATTCGCCCTATAGTGAGTCGTATTACAATTCACTGGC
                         6201                                          6250
IL13(EQ)41BBZeta  (5802) CGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTACCCAACTTA
 CD19Rop_epHIV7   (5019) CGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTACCCAACTTA
       Consensus  (6201) CGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTACCCAACTTA
                         6251                                          6300
IL13(EQ)41BBZeta  (5852) ATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAG
 CD19Rop_epHIV7   (5069) ATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAG
       Consensus  (6251) ATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAG
                         6301                                          6350
IL13(EQ)41BBZeta  (5902) GCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATG
 CD19Rop_epHIV7   (5119) GCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATG
       Consensus  (6301) GCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATG
                         6351                                          6400
IL13(EQ)41BBZeta  (5952) GAAATTGTAAGCGTTAATATTTTGTTAAAATTCGCGTTAAATTTTTGTTA
 CD19Rop_epHIV7   (5169) GAAATTGTAAGCGTTAATATTTTGTTAAAATTCGCGTTAAATTTTTGTTA
       Consensus  (6351) GAAATTGTAAGCGTTAATATTTTGTTAAAATTCGCGTTAAATTTTTGTTA
                         6401                                          6450
IL13(EQ)41BBZeta  (6002) AATCAGCTCATTTTTTAACCAATAGGCCGAAATCGGCAAAATCCCTTATA
 CD19Rop_epHIV7   (5219) AATCAGCTCATTTTTTAACCAATAGGCCGAAATCGGCAAAATCCCTTATA
       Consensus  (6401) AATCAGCTCATTTTTTAACCAATAGGCCGAAATCGGCAAAATCCCTTATA
                         6451                                          6500
IL13(EQ)41BBZeta  (6052) AATCAAAAGAATAGACCGAGATAGGGTTGAGTGTTGTTCCAGTTTGGAAC
 CD19Rop_epHIV7   (5269) AATCAAAAGAATAGACCGAGATAGGGTTGAGTGTTGTTCCAGTTTGGAAC
       Consensus  (6451) AATCAAAAGAATAGACCGAGATAGGGTTGAGTGTTGTTCCAGTTTGGAAC
                         6501                                          6550
IL13(EQ)41BBZeta  (6102) AAGAGTCCACTATTAAAGAACGTGGACTCCAACGTCAAAGGGCGAAAAAC
 CD19Rop_epHIV7   (5319) AAGAGTCCACTATTAAAGAACGTGGACTCCAACGTCAAAGGGCGAAAAAC
       Consensus  (6501) AAGAGTCCACTATTAAAGAACGTGGACTCCAACGTCAAAGGGCGAAAAAC
                         6551                                          6600
IL13(EQ)41BBZeta  (6152) CGTCTATCAGGGCGATGGCCCACTACGTGAACCATCACCCTAATCAAGTT
 CD19Rop_epHIV7   (5369) CGTCTATCAGGGCGATGGCCCACTACGTGAACCATCACCCTAATCAAGTT
       Consensus  (6551) CGTCTATCAGGGCGATGGCCCACTACGTGAACCATCACCCTAATCAAGTT
                         6601                                          6650
IL13(EQ)41BBZeta  (6202) TTTTGGGGTCGAGGTGCCGTAAAGCACTAAATCGGAACCCTAAAGGGAGC
 CD19Rop_epHIV7   (5419) TTTTGGGGTCGAGGTGCCGTAAAGCACTAAATCGGAACCCTAAAGGGAGC
       Consensus  (6601) TTTTGGGGTCGAGGTGCCGTAAAGCACTAAATCGGAACCCTAAAGGGAGC
```

```
                                 6651                                 6700
IL13(EQ)41BBZeta   (6252) CCCCGATTTAGAGCTTGACGGGGAAAGCCGGCGAACGTGGCGAGAAAGGA
 CD19Rop_epHIV7    (5469) CCCCGATTTAGAGCTTGACGGGGAAAGCCGGCGAACGTGGCGAGAAAGGA
       Consensus   (6651) CCCCGATTTAGAGCTTGACGGGGAAAGCCGGCGAACGTGGCGAGAAAGGA
                                 6701                                 6750
IL13(EQ)41BBZeta   (6302) AGGGAAGAAAGCGAAAGGAGCGGGCGCTAGGGCGCTGGCAAGTGTAGCGG
 CD19Rop_epHIV7    (5519) AGGGAAGAAAGCGAAAGGAGCGGGCGCTAGGGCGCTGGCAAGTGTAGCGG
       Consensus   (6701) AGGGAAGAAAGCGAAAGGAGCGGGCGCTAGGGCGCTGGCAAGTGTAGCGG
                                 6751                                 6800
IL13(EQ)41BBZeta   (6352) TCACGCTGCGCGTAACCACCACACCCGCCGCGCTTAATGCGCCGCTACAG
 CD19Rop_epHIV7    (5569) TCACGCTGCGCGTAACCACCACACCCGCCGCGCTTAATGCGCCGCTACAG
       Consensus   (6751) TCACGCTGCGCGTAACCACCACACCCGCCGCGCTTAATGCGCCGCTACAG
                                 6801                                 6850
IL13(EQ)41BBZeta   (6402) GGCGCGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTG
 CD19Rop_epHIV7    (5619) GGCGCGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTG
       Consensus   (6801) GGCGCGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTG
                                 6851                                 6900
IL13(EQ)41BBZeta   (6452) TTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAAC
 CD19Rop_epHIV7    (5669) TTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAAC
       Consensus   (6851) TTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAAC
                                 6901                                 6950
IL13(EQ)41BBZeta   (6502) CCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAA
 CD19Rop_epHIV7    (5719) CCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAA
       Consensus   (6901) CCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAA
                                 6951                                 7000
IL13(EQ)41BBZeta   (6552) CATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGT
 CD19Rop_epHIV7    (5769) CATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGT
       Consensus   (6951) CATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGT
                                 7001                                 7050
IL13(EQ)41BBZeta   (6602) TTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGT
 CD19Rop_epHIV7    (5819) TTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGT
       Consensus   (7001) TTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGT
                                 7051                                 7100
IL13(EQ)41BBZeta   (6652) TGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATC
 CD19Rop_epHIV7    (5869) TGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATC
       Consensus   (7051) TGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATC
                                 7101                                 7150
IL13(EQ)41BBZeta   (6702) CTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAA
 CD19Rop_epHIV7    (5919) CTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAA
       Consensus   (7101) CTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAA
                                 7151                                 7200
IL13(EQ)41BBZeta   (6752) AGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGC
 CD19Rop_epHIV7    (5969) AGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGC
       Consensus   (7151) AGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGC
                                 7201                                 7250
IL13(EQ)41BBZeta   (6802) AACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCA
 CD19Rop_epHIV7    (6019) AACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCA
       Consensus   (7201) AACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCA
                                 7251                                 7300
IL13(EQ)41BBZeta   (6852) CCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATG
 CD19Rop_epHIV7    (6069) CCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATG
       Consensus   (7251) CCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATG
                                 7301                                 7350
IL13(EQ)41BBZeta   (6902) CAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGA
 CD19Rop_epHIV7    (6119) CAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGA
```

```
       Consensus  (7301) CAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGA
                         7351                                          7400
IL13(EQ)41BBZeta  (6952) CAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGG
 CD19Rop_epHIV7   (6169) CAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGG
       Consensus  (7351) CAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGG
                         7401                                          7450
IL13(EQ)41BBZeta  (7002) GATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCAT
 CD19Rop_epHIV7   (6219) GATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCAT
       Consensus  (7401) GATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCAT
                         7451                                          7500
IL13(EQ)41BBZeta  (7052) ACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGT
 CD19Rop_epHIV7   (6269) ACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGT
       Consensus  (7451) ACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGT
                         7501                                          7550
IL13(EQ)41BBZeta  (7102) TGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAA
 CD19Rop_epHIV7   (6319) TGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAA
       Consensus  (7501) TGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAA
                         7551                                          7600
IL13(EQ)41BBZeta  (7152) TTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTC
 CD19Rop_epHIV7   (6369) TTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTC
       Consensus  (7551) TTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTC
                         7601                                          7650
IL13(EQ)41BBZeta  (7202) GGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGC
 CD19Rop_epHIV7   (6419) GGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGC
       Consensus  (7601) GGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGC
                         7651                                          7700
IL13(EQ)41BBZeta  (7252) GTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCC
 CD19Rop_epHIV7   (6469) GTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCC
       Consensus  (7651) GTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCC
                         7701                                          7750
IL13(EQ)41BBZeta  (7302) CGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACG
 CD19Rop_epHIV7   (6519) CGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACG
       Consensus  (7701) CGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACG
                         7751                                          7800
IL13(EQ)41BBZeta  (7352) AAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAAC
 CD19Rop_epHIV7   (6569) AAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAAC
       Consensus  (7751) AAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAAC
                         7801                                          7850
IL13(EQ)41BBZeta  (7402) TGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCAT
 CD19Rop_epHIV7   (6619) TGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCAT
       Consensus  (7801) TGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCAT
                         7851                                          7900
IL13(EQ)41BBZeta  (7452) TTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGAC
 CD19Rop_epHIV7   (6669) TTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGAC
       Consensus  (7851) TTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGAC
                         7901                                          7950
IL13(EQ)41BBZeta  (7502) CAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAG
 CD19Rop_epHIV7   (6719) CAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAG
       Consensus  (7901) CAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAG
                         7951                                          8000
IL13(EQ)41BBZeta  (7552) AAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGC
 CD19Rop_epHIV7   (6769) AAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGC
       Consensus  (7951) AAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGC
                         8001                                          8050
IL13(EQ)41BBZeta  (7602) TGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGA
```

```
CD19Rop_epHIV7   (6819) TGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGA
      Consensus  (8001) TGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGA
                        8051                                          8100
IL13(EQ)41BBZeta (7652) TCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGC
CD19Rop_epHIV7   (6869) TCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGC
      Consensus  (8051) TCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGC
                        8101                                          8150
IL13(EQ)41BBZeta (7702) AGATACCAAATACTGTTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTC
CD19Rop_epHIV7   (6919) AGATACCAAATACTGTTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTC
      Consensus  (8101) AGATACCAAATACTGTTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTC
                        8151                                          8200
IL13(EQ)41BBZeta (7752) AAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACC
CD19Rop_epHIV7   (6969) AAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACC
      Consensus  (8151) AAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACC
                        8201                                          8250
IL13(EQ)41BBZeta (7802) AGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAA
CD19Rop_epHIV7   (7019) AGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAA
      Consensus  (8201) AGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAA
                        8251                                          8300
IL13(EQ)41BBZeta (7852) GACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCG
CD19Rop_epHIV7   (7069) GACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCG
      Consensus  (8251) GACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCG
                        8301                                          8350
IL13(EQ)41BBZeta (7902) TGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCT
CD19Rop_epHIV7   (7119) TGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCT
      Consensus  (8301) TGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCT
                        8351                                          8400
IL13(EQ)41BBZeta (7952) ACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGG
CD19Rop_epHIV7   (7169) ACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGG
      Consensus  (8351) ACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGG
                        8401                                          8450
IL13(EQ)41BBZeta (8002) ACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAG
CD19Rop_epHIV7   (7219) ACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAG
      Consensus  (8401) ACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAG
                        8451                                          8500
IL13(EQ)41BBZeta (8052) CTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCA
CD19Rop_epHIV7   (7269) CTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCA
      Consensus  (8451) CTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCA
                        8501                                          8550
IL13(EQ)41BBZeta (8102) CCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCC
CD19Rop_epHIV7   (7319) CCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCC
      Consensus  (8501) CCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCC
                        8551                                          8600
IL13(EQ)41BBZeta (8152) TATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGC
CD19Rop_epHIV7   (7369) TATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGC
      Consensus  (8551) TATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGC
                        8601                                          8650
IL13(EQ)41BBZeta (8202) TGGCCTTTTGCTCACATGTTCTTTCCTGCGTTATCCCCTGATTCTGTGGA
CD19Rop_epHIV7   (7419) TGGCCTTTTGCTCACATGTTCTTTCCTGCGTTATCCCCTGATTCTGTGGA
      Consensus  (8601) TGGCCTTTTGCTCACATGTTCTTTCCTGCGTTATCCCCTGATTCTGTGGA
                        8651                                          8700
IL13(EQ)41BBZeta (8252) TAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAA
CD19Rop_epHIV7   (7469) TAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAA
      Consensus  (8651) TAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAA
                        8701                                          8750
```

```
IL13(EQ)41BBZeta  (8302) CGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATA
 CD19Rop_epHIV7   (7519) CGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATA
       Consensus  (8701) CGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATA
                         8751                                          8800
IL13(EQ)41BBZeta  (8352) CGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGCTGGCA
 CD19Rop_epHIV7   (7569) CGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGCTGGCA
       Consensus  (8751) CGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGCTGGCA
                         8801                                          8850
IL13(EQ)41BBZeta  (8402) CGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATG
 CD19Rop_epHIV7   (7619) CGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATG
       Consensus  (8801) CGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATG
                         8851                                          8900
IL13(EQ)41BBZeta  (8452) TGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTCCG
 CD19Rop_epHIV7   (7669) TGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTCCG
       Consensus  (8851) TGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTCCG
                         8901                                          8950
IL13(EQ)41BBZeta  (8502) GCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAA
 CD19Rop_epHIV7   (7719) GCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAA
       Consensus  (8901) GCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAA
                         8951                                          9000
IL13(EQ)41BBZeta  (8552) CAGCTATGACCATGATTACGCCAAGCTCGAAATTAACCCTCACTAAAGGG
 CD19Rop_epHIV7   (7769) CAGCTATGACCATGATTACGCCAAGCTCGAAATTAACCCTCACTAAAGGG
       Consensus  (8951) CAGCTATGACCATGATTACGCCAAGCTCGAAATTAACCCTCACTAAAGGG
                         9001                                          9050
IL13(EQ)41BBZeta  (8602) AACAAAAGCTGGAGCTCCACCGCGGTGGCGGCCTCGAGGTCGAGATCCGG
 CD19Rop_epHIV7   (7819) AACAAAAGCTGGAGCTCCACCGCGGTGGCGGCCTCGAGGTCGAGATCCGG
       Consensus  (9001) AACAAAAGCTGGAGCTCCACCGCGGTGGCGGCCTCGAGGTCGAGATCCGG
                         9051                                          9100
IL13(EQ)41BBZeta  (8652) TCGACCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAA
 CD19Rop_epHIV7   (7869) TCGACCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAA
       Consensus  (9051) TCGACCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAA
                         9101                                          9150
IL13(EQ)41BBZeta  (8702) CTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTT
 CD19Rop_epHIV7   (7919) CTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTT
       Consensus  (9101) CTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTT
                         9151                                          9200
IL13(EQ)41BBZeta  (8752) ATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTA
 CD19Rop_epHIV7   (7969) ATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTA
       Consensus  (9151) ATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTA
                         9201                                          9250
IL13(EQ)41BBZeta  (8802) GTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTTCGACGGT
 CD19Rop_epHIV7   (8019) GTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTTCGACGGT
       Consensus  (9201) GTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTTCGACGGT
                         9251                                          9300
IL13(EQ)41BBZeta  (8852) ATCGATTGGCTCATGTCCAACATTACCGCCATGTTGACATTGATTATTGA
 CD19Rop_epHIV7   (8069) ATCGATTGGCTCATGTCCAACATTACCGCCATGTTGACATTGATTATTGA
       Consensus  (9251) ATCGATTGGCTCATGTCCAACATTACCGCCATGTTGACATTGATTATTGA
                         9301                                          9350
IL13(EQ)41BBZeta  (8902) CTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATAT
 CD19Rop_epHIV7   (8119) CTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATAT
       Consensus  (9301) CTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATAT
                         9351                                          9400
IL13(EQ)41BBZeta  (8952) ATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACC
 CD19Rop_epHIV7   (8169) ATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACC
       Consensus  (9351) ATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACC
```

```
                          9401                                                9450
IL13(EQ)41BBZeta   (9002) GCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAG
 CD19Rop_epHIV7    (8219) GCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAG
       Consensus   (9401) GCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAG
                          9451                                                9500
IL13(EQ)41BBZeta   (9052) TAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGG
 CD19Rop_epHIV7    (8269) TAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGG
       Consensus   (9451) TAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGG
                          9501                                                9550
IL13(EQ)41BBZeta   (9102) TAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCC
 CD19Rop_epHIV7    (8319) TAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCC
       Consensus   (9501) TAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCC
                          9551                                                9600
IL13(EQ)41BBZeta   (9152) CCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGT
 CD19Rop_epHIV7    (8369) CCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGT
       Consensus   (9551) CCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGT
                          9601                                                9650
IL13(EQ)41BBZeta   (9202) ACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTC
 CD19Rop_epHIV7    (8419) ACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTC
       Consensus   (9601) ACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTC
                          9651                                                9700
IL13(EQ)41BBZeta   (9252) ATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGG
 CD19Rop_epHIV7    (8469) ATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGG
       Consensus   (9651) ATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGG
                          9701                                                9750
IL13(EQ)41BBZeta   (9302) ATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCA
 CD19Rop_epHIV7    (8519) ATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCA
       Consensus   (9701) ATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCA
                          9751                                                9800
IL13(EQ)41BBZeta   (9352) ATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGT
 CD19Rop_epHIV7    (8569) ATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGT
       Consensus   (9751) ATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGT
                          9801                                                9850
IL13(EQ)41BBZeta   (9402) AACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGAATTC
 CD19Rop_epHIV7    (8619) AACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGAATTC
       Consensus   (9801) AACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGAATTC
                          9851                                                9900
IL13(EQ)41BBZeta   (9452) GGAGTGGCGAGCCCTCAGATCCTGCATATAAGCAGCTGCTTTTTGCCTGT
 CD19Rop_epHIV7    (8669) GGAGTGGCGAGCCCTCAGATCCTGCATATAAGCAGCTGCTTTTTGCCTGT
       Consensus   (9851) GGAGTGGCGAGCCCTCAGATCCTGCATATAAGCAGCTGCTTTTTGCCTGT
                          9901      9914
IL13(EQ)41BBZeta   (9502) ACTGGGTCTCTCTG
 CD19Rop_epHIV7    (8719) ACTGGGTCTCTCTG
       Consensus   (9901) ACTGGGTCTCTCTG
```

FIGURE 19

IL13(EmY)-CD8h3-CD8tm2-41BB-Zeta

MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGM

GMCSFRa signal peptide IL13(EmY)

YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF

REGRFNAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAG

CD8hinge (48 aa) CD8tm(2)

TCGVLLLSLVITLYKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELGGGRVKFS

4-1BB cyto CD3ζ

RSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK

DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

GMCSFRa signal peptide
IL13(EmY)
CD8hinge
CD8 transmembrane (2)
4-1BB cyto
(Gly)3
Zeta

FIGURE 20

IL13(EmY)-CD8h3-CD28tm-CD28gg-41BB-Zeta

MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGM

GMCSFRa signal peptide IL13(EmY)

YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF

REGRFNAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVG

CD8 hinge (48 aa) CD28tm

GVLACYSLLVTVAFIIFWVRSKRSRGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSG

CD28gg

GGKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELGGGRVKFSRSADAPAYQ

4-1BB cyto CD3ζ

QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEI

GMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

GMCSFRa signal peptide
IL13(EmY)
CD8hinge
CD28 transmembrane
CD28gg
4-1BB cyto
(Gly)3
Zeta

FIGURE 21

IL13(EmY)-IgG4(HL-CH3)-CD4tm-41BB-Zeta

MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGM
GMCSFRa signal peptide IL13(EmY)

YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF

REGRFNESKYGPPCPPCPGGGSSGGGSGGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
IgG4Hinge Linker IgG4-CH3

PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN

HYTQKSLSLSLGKMALIVLGGVAGLLLFIGLGIFFKRGRKKLLYIFKQPFMRPVQTTQEEDGCS
CD4 tm 4-1BB cyto

CRFPEEEEGGCELGGGRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPE
CD3ζ

MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDA

LHMQALPPR

GMCSFRa signal peptide
IL13(EmY)
IgG4Hinge
Linker
IgG4-Fc-CH3
CD4 transmembrane
4-1BB cyto
(Gly)3
Zeta

FIGURE 22

IL13(EmY)-IgG4(L235E,N297Q)-CD8tm-41BB-Zeta

MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGM
GMCSFRa signal peptide IL13(EmY)

YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF

REGRFNESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF
IGgG4-Fc(SmP)

NWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS

KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKIYIWAPLAGTCGV
CD8 tm

LLLSLVITKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELGGGRVKFSRSADAP
4-1BB cyto CD3ζ

AYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA

YSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

GMCSFRa signal peptide
IL13(EmY)
IgG4-Fc(SmP)
CD8 transmembrane
4-1BB cyto
(Gly)3
Zeta

FIGURE 23

IL13(EmY)-Linker-CD28tm-CD28gg-41BB-Zeta

MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGM
GMCSFRa signal peptide IL13(EmY)

YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF

REGRFNGGGSSGGGSGMFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRGGHSDYMNM
Linker CD28(M) tm CD28gg

TPRRPGPTRKHYQPYAPPRDFAAYRSGGGKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFP
4-1BB cyto

EEEEGGCELGGGRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK
CD3ζ

PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ

ALPPR

GMCSFRa signal peptide
IL13(EmY)
Linker
CD28(M) transmembrane
CD28gg
4-1BB cyto
(Gly)3
Zeta

FIGURE 24

IL13(EmY)-HL-CD28m-CD28gg-41BB-Zeta

MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGM
GMCSFRa signal peptide IL13(EmY)

YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF

REGRFNESKYGPPCPPCPGGGSSGGGSGMFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRS
IgG4Hinge Linker CD28(M) tm
CD28gg

RGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSGGGKRGRKKLLYIFKQPFMRPVQT
4-1BB cyto

TQEEDGCSCRFPEEEEGGCELGGGRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDK
CD3ζ

RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTA

TKDTYDALHMQALPPR

GMCSFRa signal peptide
IL13(EmY)
IgG4Hinge
Linker
CD28(M) transmembrane
CD28gg
4-1BB cyto
(Gly)3
Zeta

Figure 25

IL13(EmY)-IgG4(HL-CH3)-CD28tm-CD28gg-41BB-Zeta

MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGM
GMCSFRa signal peptide IL13(EmY)

YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF

REGRFNESKYGPPCPPCPGGGSSGGGSGGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
IgG4Hinge Linker IgG4 CH3

PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN

HYTQKSLSLSLGKMFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRGGHSDYMNMTPRRP
CD28(M) tm CD28gg

GPTRKHYQPYAPPRDFAAYRSGGGKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEG
4-1BB cyto

GCELGGGRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK
CD3ζ

NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPP

R

GMCSFRa signal peptide
IL13(EmY)
IgG4Hinge
Linker
IgG4 CH3
CD28 transmembrane
CD28gg
4-1BB cyto
(Gly)3
Zeta

FIGURE 26

IL13(EmY)-IgG4(L235E,N297Q)-CD28tm-CD28gg-41BB-Zeta

MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGM
GMCSFRa signal peptide IL13(EmY)

YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF

REGRFNESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF
IgG4-Fc(L235E,N297Q)

NWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS

KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL

DSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKMFWVLVVVGGV
CD28(M) tm

LACYSLLVTVAFIIFWVRSKRSRGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSGGG
CD28gg

KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELGGGRVKFSRSADAPAYQQG
4-1BB cyto CD3ζ

QNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG

MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

GMCSFRa signal peptide
IL13(EmY)
IgG4-Fc(L235E,N297Q)
CD28 (M) transmembrane
CD28gg
(Gly)3
4-1BB cyto
(Gly)3
Zeta

FIGURE 27

IL13(EmY)-CD8h3-CD8tm-41BB-Zeta

MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGM

GMCSFRa signal peptide IL13(EmY)

YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF

REGRFNAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAG

CD8hinge (48 aa) CD8tm

TCGVLLLSLVITGGGKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELGGGRVK

4-1BB cyto CD3ζ

FSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ

KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

GMCSFRa signal peptide
IL13(EmY)
CD8hinge
CD8 transmembrane
(Gly)3
4-1BB cyto
(Gly)3
Zeta

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 19 17 5730

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X Y	WO 2010/025177 A1 (HOPE CITY [US]; JENSEN MICHAEL [US]) 4 March 2010 (2010-03-04) * whole document, especially the claims. * -----	1,2,4,5, 10-15 3,6-9	INV. C07K14/715 C07K14/54 C07K19/00
X	S. KONG ET AL: "Suppression of Human Glioma Xenografts with Second-Generation IL13R-Specific Chimeric Antigen Receptor-Modified T Cells", CLINICAL CANCER RESEARCH, vol. 18, no. 21, 1 November 2012 (2012-11-01), pages 5949-5960, XP055242650, US ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-12-0319 * whole document, especially page 5950 right column paragraph 3. * -----	1,10	C12N15/867 C07K14/705 C07K14/725 C07K14/73 ADD. C12N5/0783 A61K38/00
Y	MAHESH JONNALAGADDA ET AL: "Chimeric antigen receptors (CARs) incorporating mutations in the IgG4 Fc spacer region to eliminate Fc receptor recognition results in improved CAR T cell persistence and anti-tumor efficacy", JOURNAL FOR IMMUNOTHERAPY OF CANCER, BIOMED CENTRAL LTD, LONDON, UK, vol. 1, no. Suppl 1, 7 November 2013 (2013-11-07), page P18, XP021167131, ISSN: 2051-1426, DOI: 10.1186/2051-1426-1-S1-P18 * the whole document * -----	3	
	-/--		

TECHNICAL FIELDS SEARCHED (IPC)
C07K
C12N

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	13 November 2019	Kools, Patrick

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 19 17 5730

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	LIHUA E. BUDDE ET AL: "Combining a CD20 Chimeric Antigen Receptor and an Inducible Caspase 9 Suicide Switch to Improve the Efficacy and Safety of T Cell Adoptive Immunotherapy for Lymphoma", PLOS ONE, vol. 8, no. 12, 17 December 2013 (2013-12-17), pages 1-10, XP055213511, DOI: 10.1371/journal.pone.0082742 * Whole document, especially figure 1. *	6-9	
Y	JIN HEE KIM ET AL: "High Cleavage Efficiency of a 2A Peptide Derived from Porcine Teschovirus-1 in Human Cell Lines, Zebrafish and Mice", PLOS ONE, vol. 6, no. 4, 29 April 2011 (2011-04-29), page e18556, XP055175691, DOI: 10.1371/journal.pone.0018556 * abstract *	6,7	
A,D	KAHLON KANWARPAL S ET AL: "Specific recognition and killing of glioblastoma multiforme by interleukin 13-zetakine redirected cytolytic T cells", CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 64, no. 24, 15 December 2004 (2004-12-15), pages 9160-9166, XP002467417, ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-04-0454 * the whole document *	1-15	TECHNICAL FIELDS SEARCHED (IPC)

-/--

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	13 November 2019	Kools, Patrick

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 19 17 5730

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	B. THACI ET AL: "Significance of interleukin-13 receptor alpha 2-targeted glioblastoma therapy", NEURO-ONCOLOGY, vol. 16, no. 10, 10 April 2014 (2014-04-10), pages 1304-1312, XP055243094, US ISSN: 1522-8517, DOI: 10.1093/neuonc/nou045 * the whole document * -----	1-15	

TECHNICAL FIELDS SEARCHED (IPC)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	13 November 2019	Kools, Patrick

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 19 17 5730

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

13-11-2019

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010025177 A1	04-03-2010	CA 2735456 A1	04-03-2010
		EP 2331566 A1	15-06-2011
		EP 3006459 A1	13-04-2016
		ES 2553421 T3	09-12-2015
		HK 1223944 A1	11-08-2017
		JP 2012501180 A	19-01-2012
		JP 2017221211 A	21-12-2017
		US 2012148552 A1	14-06-2012
		WO 2010025177 A1	04-03-2010

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Non-patent literature cited in the description

- **CARTELLIERI et al.** *J Biomed Biotechnol 2010,* 2010, 956304 **[0003]**
- **AHMED et al.** *Clin Cancer Res,* 2010, vol. 16, 474 **[0003]**
- **SAMPSON et al.** *Clin Cancer Res,* 2014, vol. 20, 972 **[0003]**
- **BROWN et al.** *Clin Cancer Res,* 2012, vol. 18, 2199 **[0003] [0057] [0058]**
- **CHOW et al.** *Mol Ther,* 2013, vol. 21, 629 **[0003]**
- **HONG et al.** *Clin Cancer Res,* 2010, vol. 16, 4892 **[0003]**
- **BROWN et al.** *J Immunol,* 2007, vol. 179, 3332 **[0003]**
- **YAGHOUBI.** *Nat Clin PRact Oncol,* 2009, vol. 6, 53 **[0003]**
- **KAHLON et al.** *Cancer Res,* 2004, vol. 64, 9160 **[0003] [0057]**
- **KABAT et al.** Sequences of Proteins of Immunological Interest. United States Public Health Service, 1991 **[0021]**
- **EDELMAN et al.** *Proc Natl Acad Sci USA,* 1969, vol. 63, 78-85 **[0021]**
- **DEBINSKI et al.** *Clin Cancer Res,* 1999, vol. 5, 3143s **[0029]**
- **BROWN et al.** *Clinical Cancer Research,* 2012, vol. 18, 2199 **[0034]**
- **BROWN et al.** *Cancer Res,* 2009, vol. 69, 8886 **[0058]**